Neurology

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AUGUST--1955
Volume 5 — Number 8

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1. Palmer, H., and Gallagher, D. J. A.: Brit. M. J. *2*:558 (Sept. 2) 1950. 2. Ziegler, D. K., and Torres, F.: Neurology *5*:197 (March) 1955. 3. Timberlake, W. H., and Schwab, R. S.: New England J. Med. *247*:98 (July 17) 1952.

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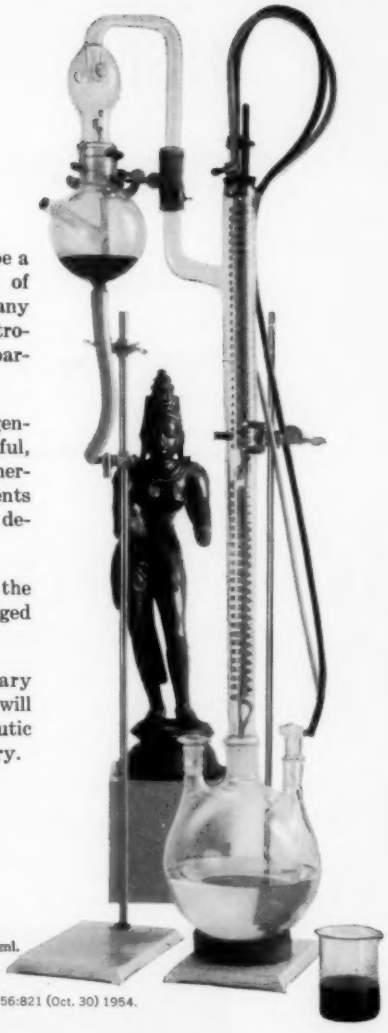

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1. Noce, R. H.: Williams, D. B., and Rapaport, W.: J. A. M. A.: 156:821 (Oct. 30) 1954.

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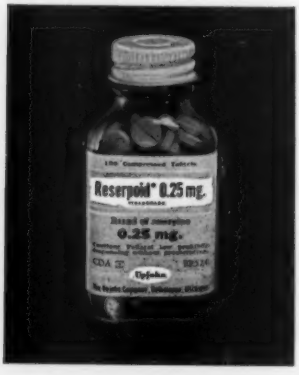

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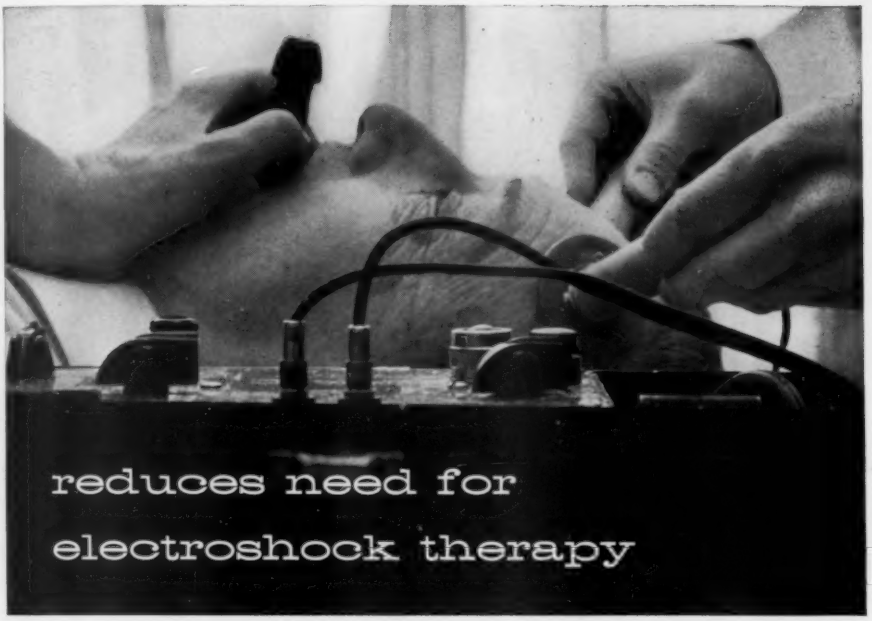

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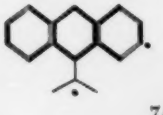

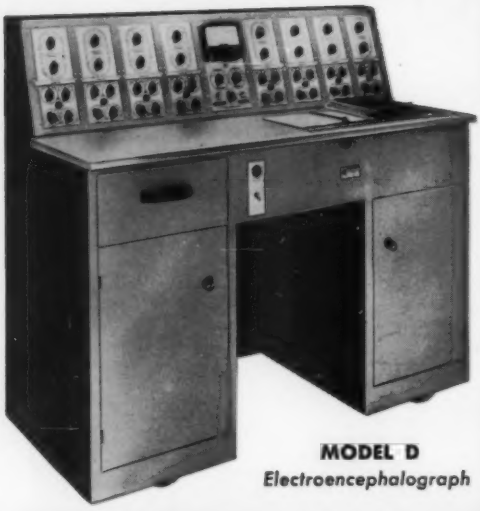

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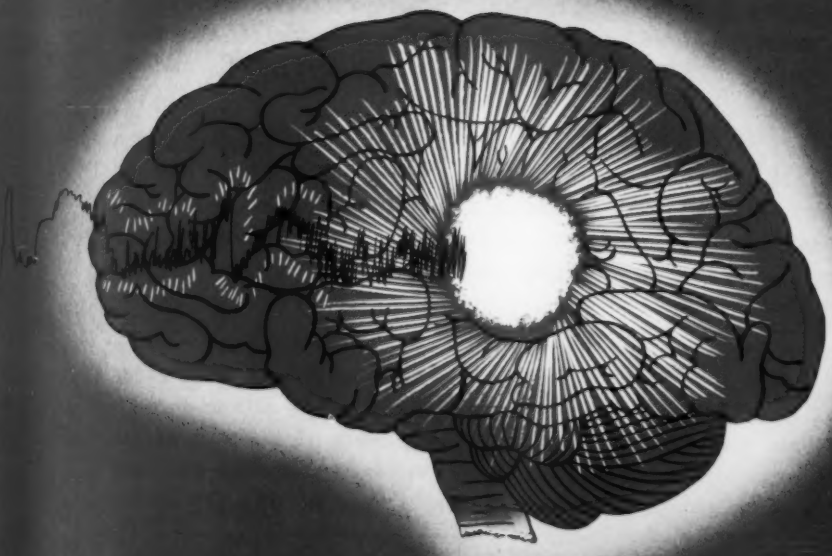

in epilepsy

NOTABLE RESULTS REPORTED WITH "MYSOLINE" IN 63 PER CENT OF PATIENTS REFRACTORY TO OTHER ANTICONVULSANTS.

The Doyle and Livingston report* covers 100 patients, mostly children, the majority ranging in age from 2 to 14 years. In 64 the epilepsy was of idiopathic origin, and in 36 it was due to organic causes. Other anticonvulsants in maximum dosages had proved ineffective in 81 of these patients for at least one year previously.

In 42 of the 81 patients who had been receiving other anticonvulsants, transition to "Mysoline" alone was completed in about 2 months; the other 39 were continued on combination therapy throughout the observation period (from 3 months to 1 year). The daily dose of "Mysoline" ranged from 0.375 Gm. to 1.5 Gm., depending on the age of the patient.

Results of therapy: "Mysoline" therapy benefited 63 per cent of the 100 patients; seizures were entirely controlled in 30, markedly reduced in 20, and moderately reduced in 13. Grand mal attacks were completely controlled in 30 of 51 patients with this type of seizure. The response in patients with petit mal, minor, or psychomotor seizures was less favorable.

Side effects: Routine blood counts and urinalyses were made on every patient and showed no abnormality at any time. No serious side reactions were observed. Drowsiness occurred in 19 per cent of the patients, sometimes with minor disturbances of equilibrium, but these side effects generally disappeared spontaneously within a few weeks.

*Doyle, P. J., and Livingston, S.: J. Pediat. 43:413 (Oct.) 1953.

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Editorial: Brit. M. J. *1*:1028 (May 1) 1954.

"Mysoline" appears to be a "relatively nontoxic drug and it did not produce any known serious side effects in a group of 48 patients." When drowsiness, dizziness, and slight ataxia were noted "these complaints ceased after reduction of the dosage. Consequently, after the proper dose was established, 'Mysoline' was well tolerated without side effects."

Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

COMPOSITE RESULTS OF 20 CLINICAL STUDIES

EPILEPTIC PATIENTS HAD FAILED TO RESPOND SUCCESSFULLY TO OTHER ANTICONVULSANTS

"Mysoline" was added to current medication which, in some cases, was eventually replaced by "Mysoline" alone.

Type of Seizure	No. of Patients	Completely Controlled	50-90% Improved	Less than 50%
Grand Mal	613	175 (28.5%)	253 (41.2%)	185 (30.3%)
Psychomotor	130	10 (7.7%)	65 (50%)	55 (42.3%)

EPILEPTIC PATIENTS HAD RECEIVED NO OTHER MEDICATION

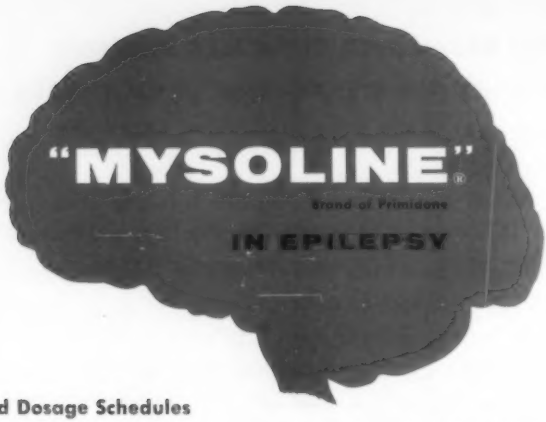
"Mysoline" alone was employed.

Type of Seizure	No. of Patients	Completely Controlled	50-90% Improved	Less than 50%
Grand Mal	214	172 (80%)	15 (7%)	27 (13%)
Psychomotor	29	19 (65%)		10 (35%)

†"Seizure discharge, the physiological basis of clinical epilepsy, is a process by which 'a portion of the cerebral nerve network (is converted) from a submaximally active asynchronous mosaic with an internal self-regulating inhibitory system to a maximally active hyperdischarging and hypersynchronized functional unit capable of detonating other regions of the brain with which it has connection'."

Kaufman, I. C., and Isenberg, S.: M. Clin. North America *36*:1381 (Sept.) 1952.

SEE NEXT PAGE FOR COMPLETE DOSAGE SCHEDULES



Suggested Dosage Schedules

Adults and children over 8 years: *In patients receiving no other anticonvulsants:* "Mysoline" therapy is started with 0.25 Gm. daily, and dosage is gradually increased at weekly intervals, until maximum therapeutic effect is achieved.

Order of Dosage Increase for Adults and Children Over 8 Years

1st week	2nd week	3rd week	4th week
0.25 Gm. (1 tablet) daily, at bedtime	0.5 Gm. (2 tablets) daily, 1 on arising, 1 at bedtime	0.75 Gm. (3 tablets) daily, in 3 divided doses	1 Gm. (4 tablets) daily, in 4 divided doses

When dosage is increased beyond 1 Gm., the daily intake is administered in four divided doses, and increments of 0.25 Gm. are added at weekly intervals as indicated above. Children 8 years and older are usually able to tolerate the same dosage as adults. ("Mysoline" is not recommended for use in dosages over 2 Gm. daily.)

In patients already receiving other anticonvulsants: "Mysoline," 0.25 Gm., is given daily and dosage is gradually increased, while the dosage of the other drug(s) is gradually decreased.

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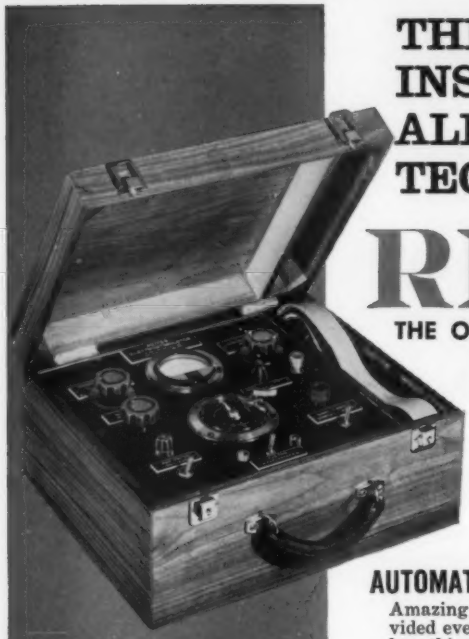

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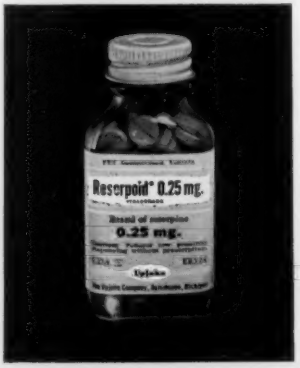

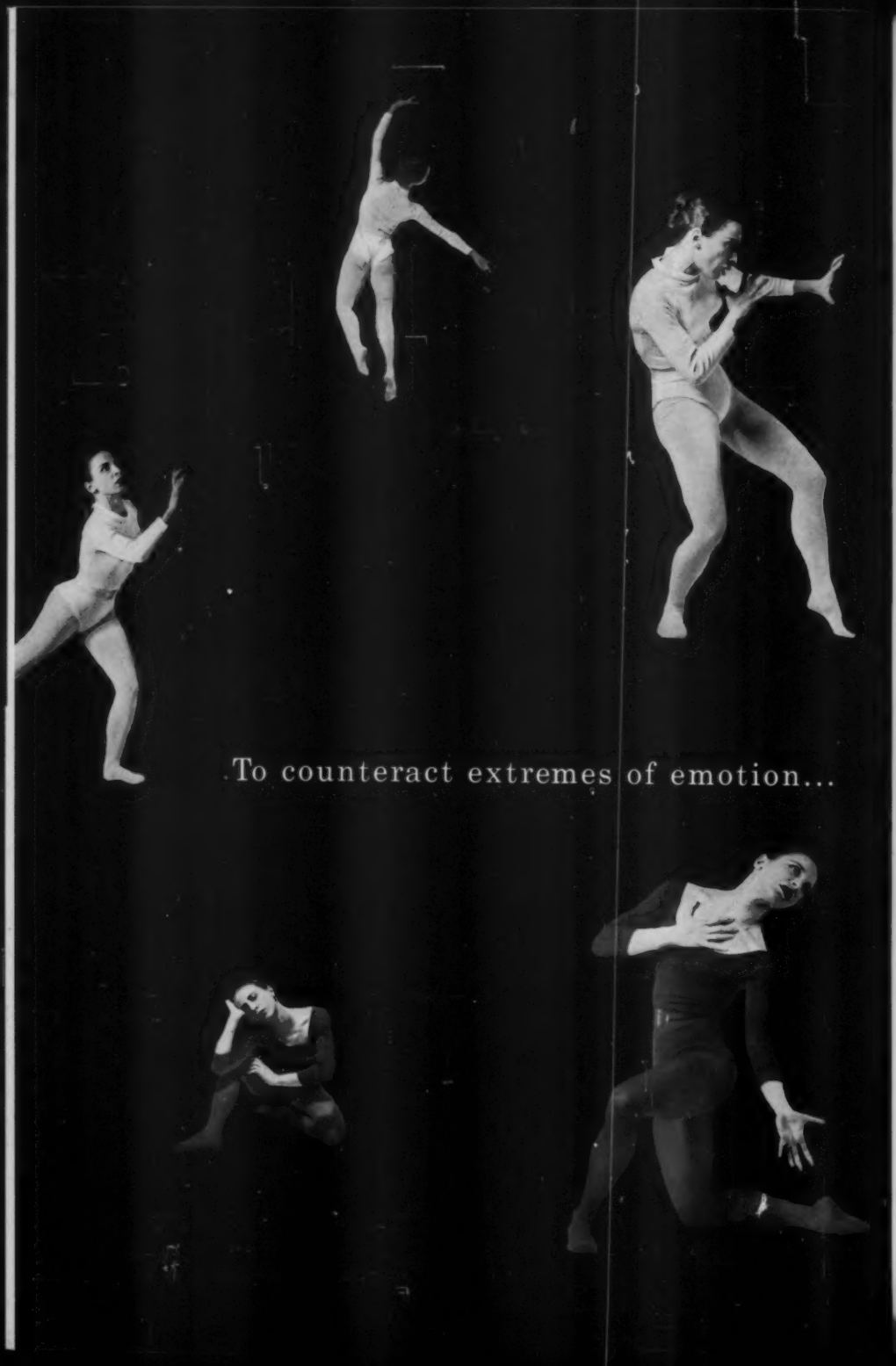
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Volume 5 Neurology Number 8

Presenile Cerebellar Ataxia in Chronic Alcoholics

S. A. Skillicorn, M.D.

CLASSIFICATION OF DEGENERATIVE DISORDERS of the cerebellar system is characterized by a variable nomenclature which has resulted in confusion for the clinician. When cerebrovascular disease, head injury, and toxic infectious processes can be eliminated as etiologic possibilities, a practical clinical approach to cerebellar ataxia is to group the cases according to genealogic record.

The hereditary ataxias[1] consist of the spinal form, Friedreich's disease, and the controversial "heredocerebellar ataxia" of Marie. A progressive familial type of cerebellar atrophy, originally described by Holmes in 1907,[2] has subsequently been designated olivocerebellar, or cerebello-olivary degeneration.[3,4] Occasional reports of transitional and intermediate forms of hereditary degenerative diseases[5–8] suggest that some of the syndromes may merely represent different manifestations of one disease process, or possibly that there is a common etiologic denominator of these disorders.[9]

Non-heredofamilial, acquired, or idiopathic cerebellar ataxia, which is the object of study in the present report, has been identified by a number of terms: olivopontocerebellar atrophy of Déjérine and Thomas,[10] delayed cortical cerebellar atrophy,[11] intracerebellar atrophy,[12] cortical cerebellar degeneration,[13] and parenchymatous cortical cerebellar atrophy.[14] Though these cases occasionally may be familial[15] or hereditary,[16] and as such, along with cerebello-olivary degeneration, probably are the histopathologic expressions of their clinical prototype, Marie's ataxia,[17–19] the majority of them reveal a normal history.

Pathologically this latter group is separated into either the cerebellipetal degeneration of olivopontocerebellar disease or the cerebellifugal cortical atrophies. It may be impossible clinically

From the department of neuropsychiatry, U. S. Naval Hospital, San Diego, California.
The opinions contained herein are those of the author and are not to be construed as official views of the Navy Department.
Author's current address: Department of Neurology, University of California Hospital, San Francisco.

to differentiate these two conditions, and even the morbid anatomic distinction between them, though often clearcut, is somewhat academic.

Six patients with a clinical picture of cerebellar atrophy, characterized by slowly progressive ataxia beginning in middle age, were admitted within a period of six months to the U. S. Naval Hospital, San Diego, California. They are presented with a two-fold purpose: 1) to emphasize that this particular syndrome should be considered in any case of progressive cerebellar dysfunction with onset in the presenium, especially if there is a history of alcoholism, and 2) to offer the concept that the cerebellar syndrome may be but part of a diffuse degenerative process of the entire brain.

CASE REPORTS

Case 1.—A single Caucasian man, aged 50, complained of progressive incoordination of his legs for one year. He admitted to heavy whiskey consumption for at least the previous two years. The family history was negative. There was no significant past history of injury or infections.

General physical examination was normal. The cranial nerves were intact. There was no nystagmus. Motor power was normal throughout. There was slight hypotonia, especially in the lower extremities. Coordination was normal in the upper extremities. The legs and trunk revealed gross ataxia and asynergia which was so severe that the patient could not stand without aid. Truncal ataxia occurred when he sat up. All forms of sensation were slightly decreased in a stocking-glove pattern over the distal portions of all four extremities. The deep reflexes were normal and equal throughout. No pathologic reflexes were noted. His sensorium was entirely within normal limits.

Complete medical studies, including chest roentgenogram, electrocardiogram, routine blood studies, blood serology, liver function tests, blood glucose, serum protein and albumin-globulin ratio, and gastrointestinal x-ray examinations were normal. Roentgenograms of the skull and electroencephalogram were normal. The cerebrospinal fluid was under a pressure of 128 mm. of water; it was clear and contained no cells; the protein was 36 mg. per 100 cc.; the colloidal gold and Wassermann reactions were negative. Pneumoencephalogram performed with replacement of 80 cc. of cerebrospinal fluid by air showed that the entire ventricular system was moderately and symmetrically enlarged. The cisterna magna was enlarged and outlined a small cerebellum.

The patient was kept under observation for six months. The peripheral sensory abnormalities subsided completely after one month of daily physiotherapy and vitamin therapy, but cerebellar signs persisted. Two weeks after the pneumoencephalogram, at which time the patient was asymptomatic except for the ataxia, he suddenly had a generalized convulsion which did not resolve spontaneously. Recurrent seizures occurred over an 18-hour period despite heroic measures to combat them, and the patient died in deep coma. Permission for a postmortem examination could not be obtained.

Case 2.—A single Caucasian man, aged 40, was admitted to the hospital in a comatose state. He had been found in a drunken stupor in a rooming house. He responded rapidly to treatment and gave a history of chronic alcoholism. He had noticed difficulty with his balance and gait for one year. In 1950 he had been discharged from the service for medical reasons, with a combined disability of bronchial asthma and paranoid state. His psychiatric disability was represented by an isolated paranoid delusional system. Family history was entirely negative. There was no significant past history of injury or infection.

Physical examination after the patient regained consciousness revealed that he was sluggish in his responses, disoriented as to time and place, and showed a considerable degree of confabulation. Other than auscultation of some pulmonary wheezing, general examination was normal. The cranial nerves were normal except for moderate dysarthria. There was no nystagmus. Muscle power and tone were normal throughout. There was no muscle atrophy. The upper extremities showed slight dysmetria and dysdiadokokinesis. Coordination in the lower extremities was grossly impaired, with an ataxic, broad-based gait, dysynergia, and dysmetria. There was marked truncal ataxia and a strongly positive Romberg test. All forms

of sensation were slightly decreased over the distal portions of all four extremities in a stocking-glove pattern. The deep muscle reflexes were normal. No pathologic reflexes were elicited.

Complete medical studies were within the limtis of normal. Blood serology was negative. An electroencephalogram and roentgenograms of the skull were normal. The cerebrospinal fluid showed a pressure of 140 mm. of water; it was clear and contained no cells; the protein was 24 mg. per 100 cc.; the colloidal gold and Wassermann reactions were negative. Psychologic studies showed an intelligence quotient of 104; the computed mental loss or deterioration was 15 per cent; the Rorschach was saturated with organic signs. Pneumoencephalogram performed with replacement of 80 cc. of cerebrospinal fluid by air revealed symmetric enlargement of the entire ventricular system as well as the basal cisterns, with evidence of cerebellar and cerebral atrophy.

During eight months of hospitalization the patient's mental picture remained essentially unchanged. His peripheral sensory changes responded rapidly to intensive vitamin therapy, so that repeat examination two months after admission showed sensation to be entirely normal throughout. However, the gross ataxia remained the same.

Case 3.—A single Caucasian man, aged 56, entered the hospital because of a traumatic left leg skin lesion which resulted from a fall. He had been a heavy drinker for many years. He had difficulty in walking and keeping his balance for one year. Family history was noncontributory. There was no significant past history of infections or head injury.

General examination revealed a small ulcer on the posterior aspect of the left leg. This was treated with antibiotics and a skin graft which took primarily, and the lesion healed completely. The cranial nerves were normal except for definite dysarthria. There was no nystagmus. The distal muscle groups of the arms and legs were slightly weak and atrophied. Muscle tone was somewhat diminished throughout. Coordination was mildly impaired in the upper extremities. There was marked incoordination of the lower extremities, so severe that the patient could not stand or walk without aid. He had a marked truncal ataxia. Sensation was diminished in all four extremities, worse distally, and in a stocking-glove pattern. The deep muscle reflexes were hypoactive throughout. No pathologic reflexes were noted. Sensorium was normal.

Routine medical studies were normal. Blood serology was negative. Roentgenograms of the skull and electroencephalogram were normal. The cerebrospinal fluid showed a pressure of 130 mm. of water; the fluid was clear and contained no cells; the protein was 32 mg. per 100 cc.; the colloidal gold and Wassermann reactions were negative. Psychologic studies revealed an intelligence quotient of 90; the computed mental loss or deterioration was 37 per cent; all testing reflected advanced organic brain disease with diverse psychologic problems and imminent psychosis. Pneumoencephalogram performed with replacement of 80 cc. of cerebrospinal fluid by air showed marked and symmetric enlargement of the entire ventricular system and basal cisterns with obvious atrophy of the cerebellum.

He was kept under observation for eight months. His peripheral neuropathy subsided promptly with intensive vitamin therapy, and repeat neurologic examinations failed to reveal any residual effects; however, marked cerebellar ataxia persisted.

Case 4.—A married Caucasian man, aged 55, entered the hospital with a dislocated left shoulder joint incurred in a fall down a flight of stairs. He gave a history of heavy alcohol intake for many years. In 1939 at the age of 40 the patient began to notice difficulty in walking, particularly with regard to balance. Over the following 15 years this condition became slowly and progressively worse. The family history was non-contributory. Past history revealed that he had suffered a minor head injury in 1930, without loss of consciousness and with no residual signs or symptoms.

General physical examination was normal. The cranial nerves were intact. There was no nystagmus or dysarthria. Muscle power was normal throughout. Slight hypotonia existed in all four extremities. There was no atrophy. The upper extremities showed slight dysmetria and dysdiadokokinesis. Coordination in the lower extremities was grossly impaired. The gait was broad-based and ataxic. Due to marked dysynergia he could hardly perform the heel-to-knee-to-toe tests. There was moderate truncal ataxia both in the sitting and standing positions. Romberg sign was strongly positive. Sensation was normal. The deep muscle re-

flexes were brisk in the lower extremities. No pathologic reflexes were noted. Sensorium was normal.

Routine medical studies were normal. Blood serology was negative. Roentgenograms of the skull revealed an old fracture of the parietal bone on the right. An electroencephalogram was normal. The cerebrospinal fluid showed a pressure of 136 mm. of water; it was clear and contained no cells; the protein was 30 mg. per 100 cc.; the colloidal gold and Wassermann reactions were negative. Psychologic studies revealed an intelligence quotient of 94; the computed mental loss or deterioration was 20 per cent; all testing reflected organic brain disease. It was concluded that he showed evidence of early mental deterioration. Pneumoencephalogram performed with replacement of 90 cc. of cerebrospinal fluid by air showed symmetric enlargement of the entire ventricular system. The cisterna magna was quite large and air outlined a small cerebellum with widened interfollial sulci.

Slight progression of his ataxia occurred over an eight-month period of observation. He suffered from repeated falls due to imbalance.

Case 5.—A single Caucasian man, aged 60, entered the hospital in a state of delirium tremens with confusional thinking, disorientation, and impaired memory. After his mental aberration subsided, he related that he had suffered from chronic alcoholism for the previous seven years. Imbalance and difficulty in walking had been present for five years and had become progressively worse. His family history was entirely negative. There was no significant past history of injury or infections.

General physical examination revealed a malnourished, psychotic patient who was confused and disoriented as to time and place. The remainder of the general physical examination was entirely normal. After a week the patient's mental state cleared completely, and thereafter there were no overt mental defects. The cranial nerves were normal. There was no nystagmus or dysarthria. Muscle power was normal. There was slight generalized hypotonia. Coordination was normal in the upper extremities, but it was grossly impaired in the lower limbs. On the heel-to-knee-to-toe test he could control neither leg sufficiently well to complete the test. Sensation was normal. The deep muscle reflexes were hypoactive. No pathologic reflexes were elicited.

Complete medical studies were normal. Blood serology was negative. An electroencephalogram and roentgenograms of the skull were normal. The cerebrospinal fluid showed a pressure of 138 mm. of water; the fluid was clear and contained no cells; the protein was 26 mg. per 100 cc.; the colloidal gold and Wassermann reactions were negative. Psychologic studies revealed an intelligence quotient of 98; his conceptualization was pathologic, and personality screenings indicated marked depressive and schizophrenic-like features; all tests revealed strong manifestations of organic brain impairment. It was concluded that there was sufficient evidence of psychotic-like ideation and organic interference to consider his disability a psychosis due to structural brain changes. Pneumoencephalogram performed with replacement of 90 cc. of cerebrospinal fluid by air showed symmetric enlargement of the entire ventricular system. Especially enlarged were the basal cisterns, revealing marked diminution in the size of the cerebellum.

His ataxia became slightly worse over a six-month period of observation.

Case 6.—A married Caucasian man, aged 50, complained of difficulty with leg coordination, which had become progressively worse since its onset two years previously. He admitted to marked overindulgence in gin and whiskey for many years. Family history was negative. There was no significant past history of injury or infections.

General physical examination was normal. The cranial nerves were normal except for slight dysarthria. There was no nystagmus. Motor power was normal throughout. There was marked hypotonia of all four extremities. There was no muscle atrophy. The upper extremities showed slight dysmetria and dysdiadokokinesis. Coordination in the lower extremities was grossly impaired, with severe dysynergia and dysmetria on the heel-to-knee-to-toe test bilaterally. There was marked truncal ataxia and a positive Romberg test. He demonstrated an ataxic, broad-based gait. Sensation was normal. The deep muscle reflexes were hypoactive to absent throughout. No pathologic reflexes were elicited.

Routine medical studies were normal. Blood serology was negative. An electroencephalogram and roentgenograms of the skull were normal. The cerebrospinal fluid showed a pressure of 110 mm. of water; the fluid was clear

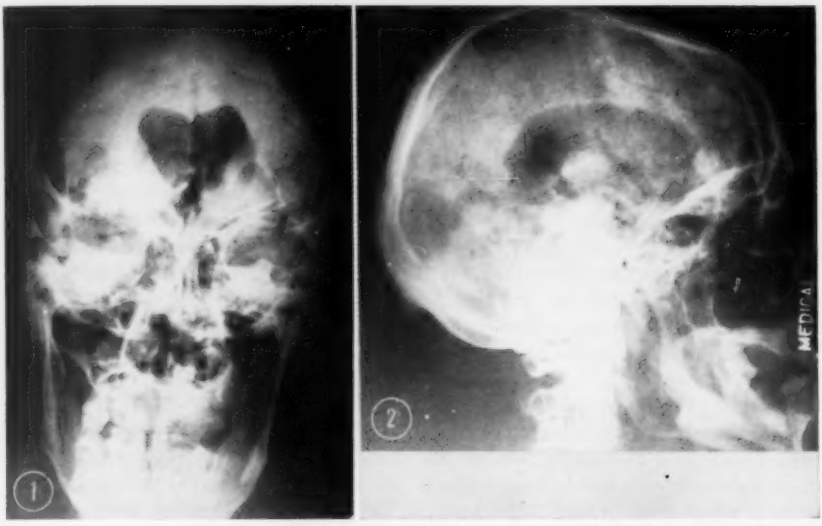

FIG. 1. Pneumoencephalogram of case 3, anteroposterior view (80 cc. exchange), showing enlarged anterior horns and bodies of the lateral ventricles with abnormally rounded contours.
FIG. 2. Lateral view in case 5, demonstrating dilated lateral ventricles. Although most of the air (80 cc. exchange) has escaped from the posterior fossa, deepened and widened interfollial sulci and fissures are shown over the superior aspect of the cerebellum.

and contained no cells; the protein was 18 mg. per 100 cc.; the colloidal gold and Wassermann reactions were negative. Psychologic studies revealed an intelligence quotient of 112; the computed mental loss or deterioration was 14 per cent; all tests reflected advanced organic brain disease with superimposed emotional instability. Pneumoencephalogram performed with replacement of 100 cc. of cerebrospinal fluid by air showed slight, symmetric enlargement of the entire ventricular system and marked dilatation of the subarachnoid channels; there was distinct widening of the interfollial sulci and fissures of the cerebellum.

His ataxia remained unchanged over a two-month period of observation.

DISCUSSION

There was a striking clinical similarity of these patients both to one another and to previously reported cases.[10–12,14] They all admitted to prolonged and excessive consumption of alcoholic beverages, and their family histories were uniformly unimportant. The gross incoordination of the trunk and lower extremities compared to the minimal involvement of the upper extremities was particularly impressive, as was the absence of nystagmus. Initially, three of the cases showed a mild to moderate peripheral neuropathy which disappeared completely following vitamin therapy and adequate diet. Their ages at the onset of the ataxia ranged from 39 to 55 years (average 47.6 years). Duration of the illness was one year for three men, two years for one, five years for one, and 15 years for the other. One patient died in status epilepticus at age 50 after he had been ataxic for one year.

A satisfactory explanation has never been given for the predominance of cere-

bellar dysfunction in the lower extremities in this syndrome. In the numerous contributions to the anatomy and physiology of the cerebellum there have been conflicting conclusions as to localization of function within this structure,[20–26] except for the established fact that there is ipsilateral synergic control of the limbs. Some investigators have presented the concept that there is considerable cerebellar influence on the various cerebral, diencephalic, mesencephalic, and medullary centers, and that this influence may be exerted in such a way as to potentiate or to suppress their activity, depending upon their physiologic needs for proper function.[27,28] The evolutional transition from four-legged to upright two-legged animal ambulation possibly has resulted in redistribution of cerebellar function, that is, adaptation, with functional activity directed toward maintenance of synergy more in the lower than in the upper extremities, and with consequent prevalence of leg incoordination in cases of diffuse degeneration of the cerebellum. The absence of nystagmus probably indicates that the vestibular nuclei and their connections are not involved by the degenerative process, at least not of sufficient extent to produce clinical manifestations.

Atrophy of the cerebellum is reflected by distinct pneumoencephalographic changes.[29] In this study each case showed marked enlargement of the cisterna magna and fourth ventricle with diminution in size of the cerebellum, as well as deepened and widened interfollial sulci and fissures. These abnormalities were best demonstrated during early stages of the fluid-air exchange (20 to 40 cc.) with the patients in the upright position, and after further exchange (80 to 100 cc.) they were most prominent in the brow-down view.

To diagnose atrophy of the cerebral hemispheres on the basis of air-studies alone may be a precarious inference, especially if only partial replacement of cerebrospinal fluid by air is performed. Nevertheless, the dilatation and rounded contour of the ventricles and widening of the subarachnoid sulci in each of these cases was of sufficient degree to establish the impression of cerebral atrophy (figures 1 and 2).

The electroencephalogram was normal in all six patients. Though transient abnormalities similar to those resulting from temporary cerebral hypoxia[30,31] may occur during acute alcoholic intoxication,[32] they are relatively uncommon in chronic degenerative brain disease.

Psychologic evaluation of five of the patients revealed definite manifestations of organic brain impairment of a deteriorative type. This tended to substantiate the pneumoencephalographic diagnosis of diffuse cerebral cortical degeneration. Clinically there was evidence of mental disease in one patient (case 2) in the form of delusions and confabulation, while another patient (case 5) exhibited a transient episode of disorientation and acute psychosis associated with delirium tremens. Both of these men demonstrated obvious evidence of psychosis on psychologic testing. Four cases clinically showed no overt mental defects, although one (case 3) did present incipient signs of psychosis on psychologic investigation. One patient expired before these studies were performed. The tests administered were: M.M.P.I., sentence completion, draw-a-person, drawing completion, Rorschach, Bender-Gestalt, Grayson perceptualization, Goldstein-Sheerer-Weigl, Shipley-Hartford, and Wechsler-Bellevue Form I.

Although the etiology of cerebellar atrophy remains obscure, a few observations should be made. Sensitivity to some drugs is occasionally manifested by transient cerebellar dysfunction, especially in children. There have been many reports of cerebellar damage resulting from the hyperpyrexia of sunstroke,[33] heatstroke,[34–36] acute rheumatic fever,[37] post-thyroidectomy crisis,[38] and hypersensitivity reactions.[39,40] It has been established that the Purkinje cells have relatively brief survival times in the presence of anoxemia.[41,42] Chronic alcoholism has been implicated as a possible factor in the development of cerebellar atrophy by several investigators.[12,13,43] Experimental studies have revealed that alcoholic intoxication in animals results in destruction of Purkinje cells.[13] It is conceivable that alcohol consumption over a prolonged period, perhaps with associated dietary deficiencies and chronic hypoxemia, likewise may result in permanent cellular damage within the human cerebellum in susceptible individuals.

The microscopic findings in cases of cortical cerebellar atrophy consist of considerable loss of Purkinje cells and thinning of the granular layer, with preservation of the basket cells.[44] In addition to the cerebellar involvement, histologic changes occasionally may occur in the spinal cord, brainstem, basal ganglia, and subthalamic nuclei;[43,45] and the cerebellar ataxia may be associated with or replaced by signs of more diffuse central nervous system disease, particularly of extrapyramidal origin.

Intellectual deterioration sometimes progressing to dementia is not uncommon in this condition,[4] and such cases may demonstrate cerebral degeneration. Thus, involvement of portions of the brain other than the cerebellar system justifiably might be anticipated in cases of cerebellar atrophy. The degree of such involvement does not necessarily correlate with the stage of the patient's illness, since the duration of symptoms in the present cases ranged from one to 15 years, while their clinical findings were quite similar at the time of evaluation.

Although the present report is lacking pathologic verification, it has been concluded on the basis of markedly dilated lateral ventricles as shown by air studies, psychologic evidence of organic brain impairment, and neurologic and pneumoencephalographic findings of cerebellar atrophy that clinically these cases represent diffuse cerebrocerebellar cortical degeneration.

SUMMARY

A report is given of a slowly progressive cerebellar dysfunction occurring in six males in the presenium, with predominant ataxia of the lower extremities and negative family histories. Age at onset of symptoms varied from 39 to 55 years (average: 47.6 years). Duration of the illness was one year for three men, two years for one, five years for one, and 15 years for the other.

All patients admitted to prolonged overindulgence in alcoholic beverages. Three of them initially had a peripheral neuropathy which subsided on treatment. Nystagmus was absent in all cases.

Pneumoencephalographic and psychologic studies suggested the presence of diffuse degenerative disease of the cerebrum, in addition to cerebellar atrophy.

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Multiple Intracranial Expanding Lesions of Diverse Origin

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Exclusive of von Recklinghausen's disease, metastatic malignancy, and abscess, the occurrence of two intracranial tumor masses in the same individual is distinctly unusual. Multiple meningiomas, gliomas, neurinomas, hemangioblastomas, as well as varying combinations of growths have been reported. The literature dealing with multiple intracranial neoplasms up to 1946 was briefly summarized in a previously published article.[1] A number of additional reports have since appeared. Alexander[2] described a case in which a meningioma of the right frontal lobe together with a spongioblastoma ependymale was found in the roof of the left lateral ventricle. The association of a cerebral meningioma and oligodendroglioma lying in juxtaposition was recorded by Gass and van Wagenen.[3] The presence of a meningioma of the optic nerve together with multiple glioblastomas of the corpus callosum and temporal lobe in the same patient was observed by Brihaye, Davis, and Drochmans.[4] A case in which there existed both a cerebellopontine angle meningioma and a contralateral cerebral astrocytoma was reported by Hoffman.[5] In relating his experience with intracranial meningiomas, Fincher[6] included two cases of multiple tumors of different histologic nature. In one, a left frontoparietal meningioma developed in a patient known to have a right temporal astrocytoma. The second case was that of a patient who had both a glioblastoma multiforme and a meningioma on the same side of the brain. In a paper on familial hemangioblastomas, Craig and Horrax[7] included the protocol of a patient with two such tumors, one in each cerebellar hemisphere. Further examples of multiple gliomas were contributed by Lamartine de Assis and associates,[8] Carl,[9] and Manzini and Serra.[10] Wise, Malamud, and Boldrey[11] reported two cases of cerebral oligodendroglioma occurring in association with a chromophobe adenoma of the pituitary.

Except for the few cases in which the presence of more than a single tumor was unsuspectingly disclosed at operation, the diagnosis of multiple primary neoplasms, other than those belonging in the von Recklinghausen category, has almost invariably been established at necropsy. In 1947 the author, together with Davidoff,[1] reported a case in which two intracranial tumors of varying origin were recognized and verified during life. One of the growths was a meningioma arising from the falx, the other

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a glioblastoma multiforme situated in the opposite cerebral hemisphere. Since then, two additional cases of multiple intracranial expanding lesions of diverse origin have been encountered, in both of which the dual nature of the underlying pathology was demonstrated in living subjects. In one patient there existed both a hyperostosing sphenoid wing meningioma and a glioblastoma multiforme located in the ipsilateral frontal parasagittal region. A glioblastoma multiforme situated in the parietal region at the exact site of an abscess removed six years earlier was found in the second case. A report of these two cases together with a summary of the case previously described follows.

Case 1.—Unilateral proptosis followed by a focal seizure and hemiparesis in a 54 year old male. Radiologic evidence of a sphenoid wing meningioma. Persistence of focal neurologic deficit and headache following craniotomy for meningioma. Pneumoencephalographic evidence of a parasagittal tumor on the same side. Disclosure of a glioblastoma multiforme at second operation.

History: A 54 year old right-handed salesman was admitted to the hospital on November 26, 1950 because of right-sided weakness. For several months prior to admission he complained of pain about the left eye and more recently protrusion of that eye had become apparent. On November 1, 1950 he experienced a seizure beginning in the right hand and spreading to the elbow. Similar episodes occurred on a number of occasions during the following week. About this time too he became aware of weakness of the right upper extremity. This became more pronounced and eventually the right lower limb was also affected.

Physical examination: In addition to a right hemiparesis more pronounced in the upper extremity, the patient exhibited a nominal speech defect, difficulty in computation, and a disturbance in body scheme. The deep tendon reflexes were more active on the right, in addition to which an extensor plantar response was demonstrable on that side. All modalities of sensation appeared to be intact. No visual field defect was demonstrable by confrontation. The fundi were normal. The left eye was proptosed and its upper lid edematous. Otherwise the general physical examination revealed no abnormalities.

Laboratory data: Routine blood and urine studies disclosed normal findings. Blood serology was negative. Roentgenograms of the skull revealed a considerable increase in density of bone about the left orbit, characteristic of a pterional meningioma (figure 1). The structures involved included the roof of the orbit, the greater and lesser wings of the sphenoid, and the squamous portion of the temporal bone. There was no atrophy of the sella turcica and the pineal body was not displaced. A roentgenogram of the chest showed no abnormality. Electroencephalography demonstrated a small amount of slow wave activity in the left frontotemporal region and, to a lesser degree, in the right temporal area.

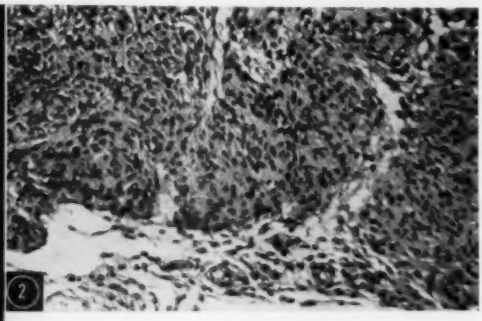
Operation 1: It was recognized that the degree of neurologic deficit was unusual for a meningioma originating from the outer third of the sphenoid ridge. The roentgen changes were nevertheless characteristic of a hyperostosing meningioma at this site and accordingly operation was undertaken. On November 30, 1950 a left frontotemporal craniotomy was performed. The presence of a meningioma "en plaque" with extensive involvement of the sphenoid wing was confirmed. A considerable amount of the cranial hyperostosis was removed, the orbit decompressed, and the thin intradural growth excised. The latter measured about 1 cm. by 2 cm., its maximal thickness being approximately 0.5 cm. Obviously the extensive neurologic deficit could hardly be attributed to the insignificant intradural portion of the tumor.

Histology: Microscopic examination of the growth and its dural attachment disclosed whorls of meningocytes interspersed in loose areolar tissue containing numerous mature vessels and vascular spaces. Clusters of tumor cells were also observed within the tissue spaces of the dura (figure 2). Histologic study of the bone fragments revealed the presence of scattered whorls and nests of meningocytes.

Course: For about two weeks following operation, the patient was unable to speak and the hemiparesis was more pronounced. During this period also focal seizures involving the

limbs on the right reappeared. He regained his speech toward the middle of December and began to complain of left-sided headache. Lumbar puncture revealed colorless cerebrospinal fluid under a pressure of 180 mm. water, containing 90 mg. per cent protein. The headache persisted and became more distressing. Early in January 1951, a severe degree of focal abnormality affecting the left frontotemporal region was evident in the electroencephalogram. Further investigation was clearly indicated, and on January 8, 1951 a pneumoencephalogram was performed. The ventricles were observed to be displaced to the right of the midline and the left frontal horn was depressed (figure 3). These findings indicated the presence of a parasagittal tumor in the left frontal lobe.

Operation 2: On January 10, 1951 a more extensive exposure of the left frontal lobe was



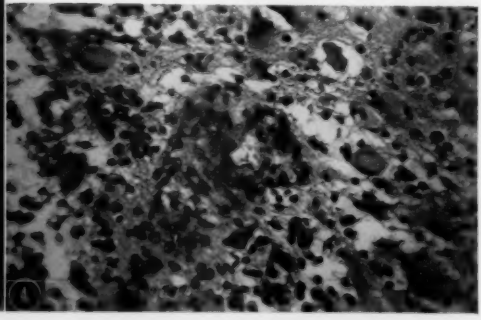


FIG. 1. *Case 1.* Thickening of bone about left orbit, including roof, sphenoid wings, and squamous part of temporal bone.

FIG. 2. Appearance of intradural component of tumor removed at first operation.

FIG. 3. Ventricular displacement away from side of operation.

FIG. 4. Tumor removed at second operation. Typical structure of a glioblastoma multiforme.

undertaken. The medial margin of the brain was explored without disclosing a surface tumor. The superior frontal convolutions were widened and softened, suggesting the presence of a subcortical neoplasm. At a depth of about 3 cm. canary yellow fluid was aspirated. A block of cortex was excised and at the anticipated distance below the surface of the brain, a friable, yellowish-brown tumor extending into the corpus callosum was encountered. An incomplete removal was accomplished.

Histology: The microscopic features were those of a glioblastoma multiforme. Cells of varying size and shape, including multinucleated giant forms, were present. Mitotic figures were observed. Areas of necrosis and of hemorrhage, pseudopalisade formation, cystic degeneration, and vascular proliferation were conspicuous (figure 4).

Subsequent course: The hemiparesis and aphasic manifestations persisted. Radiation therapy was administered without benefit. Death occurred on August 18, 1951, seven months after the second operation.

Case 2.—Progressive aphasia, right hemiparesis, and evidence of increased intracranial pressure in a 40 year old female. Removal of brain abscess followed by considerable improvement. Recurrence of symptoms six years later. Pneumoencephalographic demonstration of a recurrent mass. Glioblastoma multiforme disclosed at site of original operation.

History: A 40 year old right-handed woman entered the hospital on October 2, 1945, complaining of headache, vomiting, and impairment of vision and speech. Some four months previously a subtotal gastrectomy had been performed for a peptic ulcer. Shortly after this operation she began to experience throbbing occipital headache and often vomited. Subsequently her right hand became weak and she began to experience difficulty in expressing herself. Eventually vision became blurred and she consulted an ophthalmologist who referred her to the hospital.

Physical examination: A pronounced degree of aphasia involving both receptive and emissive speech was evident. The right side of the face and the right upper extremity were paretic and the protruded tongue deviated toward the right. The deep tendon reflexes were more active on the right and a positive Babinski toe sign was demonstrable on that side. Only the left upper abdominal reflex was elicited. The peripheral visual fields appeared to be intact. Funduscopic examination revealed a severe degree of bilateral papilledema.

Laboratory data: The blood and urine examinations disclosed no abnormalities. The blood Wassermann reaction was negative. A roentgenogram of the chest showed nothing unusual. X-rays of the skull revealed slight atrophy of the posterior clinoids. Electroencephalography demonstrated bilateral abnormalities affecting the left side to a greater degree, but without any focal accentuation.

Operation: A ventriculogram was performed on October 8, 1945. The ventricular system was observed to be markedly displaced to the right and the roof of the posterior half of the body of the left lateral ventricle was depressed. These findings indicated the presence of a mass in the left parieto-occipital region. At operation a circumscribed, hard, pinkish-gray tumor measuring about 4 cm. in all directions and attached to dura near the longitudinal sinus was exposed (figure 5). The lesion was totally removed, including its dural attachment. On sectioning it proved to be an old encapsulated abscess. Gram positive cocci were observed in a stained smear. The organism was subsequently identified as a *Staphylococcus aureus.*

Histology: The abscess cavity was lined by many reticuloendothelial cells and relatively few polymorphonuclear leukocytes. Its wall consisted of an inner and outer layer, the former staining more deeply with hematoxylin and eosin (figure 6). Mononuclear cells, plasma cells, lymphocytes, and eosinophils were present, separated in places by connective tissue (figure 7). Numerous vascular channels and proliferating vessels were observed, as well as large numbers of compound granular corpuscles. Inflammatory cells, mostly lymphocytes, were present about some of the blood vessels in the outer layer.

Course: Penicillin and sulfadiazine were administered postoperatively. Considerable improvement occurred in both speech and motor function. A homonymous hemianopia was discernible at this time.

Following discharge from the hospital, she continued to do well and eventually was able to fully resume her usual household activities. Once or twice a year she had a seizure.

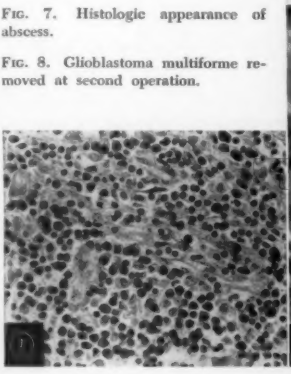
In June 1951, approximately six years after her operation, she returned to the clinic be-

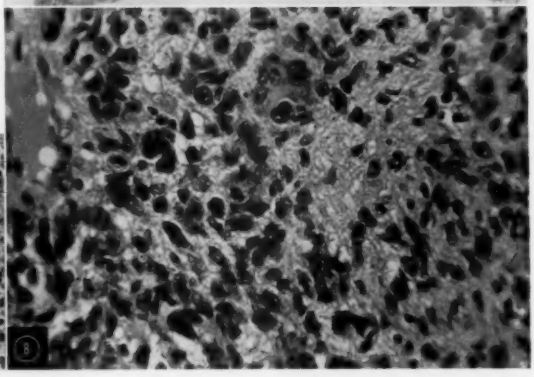
FIG. 5. *Case 2.* Gross appearance of abscess removed at first operation.

FIG. 6. Low power section of abscess wall.

FIG. 7. Histologic appearance of abscess.

FIG. 8. Glioblastoma multiforme removed at second operation.





cause of an increase in the frequency of the convulsions. The fits were focal in nature, beginning in the right foot and spreading to involve the entire right lower extremity. Following a seizure the affected limb was temporarily paretic. Neurologic examination at this time disclosed a right homonymous defect, a slight right-sided hyperreflexia, absence of the abdominals on the right, and an equivocal right plantar response. Speech was intact and there was no obvious weakness. The possibility of a recurrence of the brain abscess was suspected, and when an increase in the dose of anticonvulsant medication failed to control the seizures, further studies were deemed advisable. Electroencephalography revealed a focal abnormality. A pneumoencephalogram disclosed no displacement of the ventricles but the roof of the posterior half of the body of the left lateral ventricle was slightly depressed. The cerebrospinal fluid protein content was 76 mg. per cent. The pattern of seizures changed in that the right upper extremity now was also involved. Following one such convulsion, she remained hemiparetic.

Operation 2: On August 29, 1951 the bone flap was reelevated. Precisely at the site of the previous lesion in the parasagittal parietooccipital region, a greyish-pink tissue was encountered which extended deeply into the white matter and which had the appearance of an infiltrating neoplasm. A gross total removal was accomplished.

Histology: Microscopic examination revealed all the elements of a glioblastoma multiforme (figure 8). The tissue was highly cellular and contained large numbers of blood vessels. The cells varied considerably as regards size, shape,

and staining characteristics, though most were large, dark, and irregular or elongated in outline. Mitotic figures were observed. There were also present areas of band-like necrosis, as well as a marked hyperplasia of the endothelial and adventitial cells of the blood vessels.

The sections of the specimen removed at the first operation were reviewed and a diagnosis of Hodgkin's disease suggested by one pathologist. The slides were then submitted to a number of other pathologists, all of whom concurred in the original diagnosis of brain abscess. There was no disagreement as to the nature of the lesion removed at the second operation.

Subsequent course: The patient improved following operation but eventually manifested evidence of recurrence and expired at home on March 4, 1952. A necropsy was not performed.

A detailed report of the third case having already been published,[1] it will be presented in summarized form.

Case 3.—A 58 year old female was admitted to the hospital on April 19, 1946 because of headache of 15 months' duration. Neurologic examination revealed only early papilledema. Ventriculography disclosed evidence of a right frontal tumor, and at operation a parasagittal meningioma arising from the falx was found. A total removal was accomplished and the diagnosis confirmed histologically. The patient failed to improve postoperatively, however, and subsequently displayed considerable mental deterioration. Eventually evidence of increased intracranial pressure reappeared. Pneumoencephalography was repeated, demonstrating the presence of an expanding lesion on the left side. At operation a cystic glioma of the left frontal lobe was exposed and biopsied. Histologically it proved to be a glioblastoma multiforme.

COMMENT

The occurrence of multiple intracranial tumor masses of diverse origin is infrequent and poses a difficult diagnostic problem. Usually the diagnosis is established unexpectedly at necropsy. It appears possible, however, in some instances at least, to recognize the presence of multiple lesions during life. An awareness of the fact that more than one tumor may occur in the same individual simultaneously or at different times is prerequisite. The existence of more than one intracranial mass may be suspected on the basis of the clinical data. As an example, in Cushing and Eisenhardt's monograph[12] there is included in the section on peritorcular meningiomas a case in which there also existed a glioblastoma of the corpus callosum. Despite the known presence of a meningioma visible in the roentgenograms as a calcified tumor at the occipital pole, another lesion, a malignant subcortical glioma, was correctly anticipated in view of the clinical manifestations of a rapidly progressive hemiplegia and aphasia.

More commonly perhaps, failure to improve postoperatively as anticipated or an unexpected recurrence of symptoms following the removal of a benign growth should suggest the possibility of another independent lesion and lead to further investigation. It was precisely this kind of reasoning which led to the disclosure of multiple tumor masses in the cases reported. Admittedly, in case 1 it was recognized at the very outset that the extent of neurologic deficit was unusual for a hyperostosing pterional meningioma, and in case 3 a recurrent abscess was suspected. In any event the indications for further clarification of the clinical phenomena were clearly appreciated in all three cases.

It must also be admitted that the element of chance plays a part in determining the course of events in such cases. Should the initial symptomatology lead to the demonstration of the presence of an infiltrating glioma, particularly one of the more malignant variety, it is hardly likely that the possibility of another type of lesion would subsequently be entertained or its existence verified during life. For example, in one of Fincher's

cases, in which a left cerebral meningioma developed in a patient with a right temporal astrocytoma known to have already involved the region of the third ventricle, the appearance of an ipsilateral hemiparesis (right) was justifiably ascribed to invasion of the left hemisphere by the astrocytoma.

The occurrence in case 2 of a glioblastoma multiforme at the very site of previous brain abscess probably was an unusual coincidence. Any digression into the question of a causal relationship would be sheer speculation. The author is unaware of any similar case in the literature, though Bailey[13] in 1942 did describe a sarcoma of the temporal lobe associated with abscess formation. He expressed the belief that the infection bore no relation to the origin of the tumor.

SUMMARY

Three cases of multiple intracranial tumor masses of diverse origin are reported in which the lesions were recognized and verified during life. The presence of more than one intracranial growth may at times be suspected on the basis of the clinical data. Failure to improve postoperatively as expected or a recurrence of symptoms following the removal of a benign tumor should suggest the possibility of another independent lesion.

The author wishes to express his thanks to Dr. Leo M. Davidoff for permission to use his case material and for his many helpful suggestions.

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Measurement of Quadriceps Reflex in Spastic Paralysis

Philip S. Bergman, M.D., Gerald G. Hirschberg, M.D. and Morton Nathanson, M.D.

IT IS OFTEN DIFFICULT to determine clinically whether a "hyperactive" deep reflex is normal or abnormal. The history and the associated positive findings are usually necessary to make this distinction. The purpose of this investigation was to learn whether the electrical characteristics of the reflexes were distinctive enough to differentiate the normal from the abnormally active reflex.

The quadriceps reflex (knee jerk) was evaluated by observing the action potential of the quadriceps femoris during reflex activity induced by a constant stimulus to the patellar tendon. The electrical pulse emitted when this muscle is suddenly stretched is relatively simple in form and presumably represents synchronous activity of motor units, the size of the potential being determined by the number of such units contracting synchronously at one time.

Reinforcement of reflexes, by such means as the Jendrassik maneuver, is used clinically to elicit reflexes that are unobtainable without it. In the Jendrassik maneuver, the patient grasps the curled fingers of both hands, one with the other, attempting to pull the hands apart. This has not been used systematically in the study of normal and hyperactive reflexes, however, and it appeared to offer a method of comparing the extremities of the paralyzed patient with those of normal subjects.

MATERIAL AND METHOD

The subjects included 25 normal individuals, 27 patients with spastic hemiplegia or hemiparesis due to cerebrovascular accident, and 17 patients with spastic paraparesis (six due to trauma, and 11 as a result of multiple sclerosis). The abnormal subjects had all had weakness of one or more extremities for several weeks or months and had presumably reached some clinical stability.

The subject was seated on the edge of a table, his legs swinging freely. The stimulus was applied by striking the patellar tendon with a specially designed hammer (figure 1). The force of the blow was constant for all the subjects and represented the maximum thrust of which the device was capable. The action potentials were picked up by two broad metal plates (electrocardiogram electrodes) applied to the skin over the

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FIG. 1. Method of eliciting reflexes. Two steel plates (electrocardiograph electrodes) are applied to the skin over the quadriceps muscle. The plunger of the gun held by the experimenter strikes the patellar tendon and the overlying strip of tape which contains a simple switch to trigger the oscillograph sweep. The patient is lifting a weight to induce reinforcement.

quadriceps femoris. The skin resistance was reduced to less than 1000 ohms by lightly abrading the epidermis with sandpaper; contact was established with the use of electrode jelly and the electrode held in place by broad rubber straps. The patient was grounded by a separate electrode. The recording electrodes were connected, through a preamplifier, with a conventional cathode-ray oscillograph. The traces were photographed and measurements (peak-to-peak) made from the photographic negatives. A simple switch (two copper strips) was taped to the skin over the patellar tendon at the point of impact, and incidentally served to restrict this point accurately in repeated trials. The closing of this contact by the blow of the hammer activated a circuit through a 1.5 volt dry cell, which initiated a single sweep of the oscillograph. During this sweep the muscle action potential appeared. The latency time of the electrical response was represented by the interval from the beginning of the sweep to the beginning of the action potential.

As a substitute for the Jendrassik maneuver, the subject lifted a weight with one hand, shortly before the reflex was elicited, so that the same type of reinforcement could be carried out by normal and hemiplegic patients. At least 30 reflexes were observed on each side, ten without reinforcement and ten each with reinforcement of a five- and ten-pound weight, respectively. Thus at least 60 observations were made on each subject. Some subjects were asked not to lift the weight when the command was given, and the reflex was then ex-

amined as though the weight had been lifted in the usual way. Sometimes the effect of events which distracted the attention of the subjects were used as reinforcement, such as the ringing of a telephone or attempts at levity. The effect of reducing the movement of the leg by manual restraint was also studied. A minimal value was obtained, which consisted of the smallest amplitude recorded, after elimination of the lowest 25 per cent of the observations known or presumed to be caused by technical error. A maximal value was the highest amplitude obtained, with or without intentional reinforcement. Mean values were used in the statistical studies, which were carried out according to standard technics.

Although electrical recording is no better than mechanical measurement of knee jerks in normal subjects (they were, in fact, found to be comparable in preliminary studies), in spasticity there is often considerable disparity between the swing of the leg and the muscle potential. In such instances, the electrical record corresponds to the observed contraction of the muscle and justifies the use of what may seem to be an unnecessarily complicated method. After it had been established that the latency and the wave form were not significant variables, some recordings were made on an ink-writing oscillograph, which appeared to be satisfactory.

RESULTS

Amplitude of the Action Potential.

The values obtained in the various classes of subjects under different conditions are shown in table 1.

Normal subjects (24 cases): Without reinforcement the quadriceps action potential had an amplitude of from 50 to 2200 microvolts, with a mean of 603 microvolts. The potentials with reinforcement varied from 50 to 3070 microvolts, with a mean of 995 microvolts. The effect of reinforcement was highly significant statistically. ($P < .01$).

Hemiplegia (27 cases): 1) *Nonparetic ("normal") side:* Without reinforcement the potentials varied from 35 to 6500 μv., with a mean of 1325 μv. After reinforcement the range was from 100 to 7500 μv., with a mean of 1455 μv. The effect of reinforcement was not significant. 2) *Involved side:* Values without reinforcement varied between 50 and 9000 μv., with a mean of 2479 μv. With reinforcement the range was from 100 to 7500 μv., mean 2369 μv. Reinforcement, then, had no significant effect. Because of great variability between individuals, group differences between the two sides were not statistically significant, with or without reinforcement, although in each subject the response on the paralyzed side was always greater than that in the opposite extremities. Also because of variability, there was no significant difference between the nor-

TABLE 1

AMPLITUDE OF ACTION POTENTIALS OF QUADRICEPS REFLEXES (IN MICROVOLTS) IN VARIOUS CONDITIONS, WITH AND WITHOUT REINFORCEMENT

	Without Reinforcement			*With Reinforcement*		
	Minimum	*Mean*	*Maximum*	*Minimum*	*Mean*	*Maximum*
Normal	50	603	2200	50	995	3070
Hemiplegia, affected side	50	2479	9000	100	2369	7500
Hemiplegia, unaffected side	35	1325	6500	100	1455	7500
Traumatic paraplegia	30	1784	7000	30	1902	6600
Multiple sclerosis	160	3644	10,000	200	3631	7600

mals and either side of the hemiplegics, regardless of reinforcement. The statistical methods used took into account variations between individuals as well as variability of separate measurements in the same subject. For this reason, since the normal group showed such wide fluctuations, none of the comparisons which involved the normals was significant. However, comparisons in which variability was the factor being assessed showed significant differences between the responsiveness of the normals to reinforcement and the lack of it in the patients. Statistical validation could be obtained only for the effect of reinforcement in the two groups, that is, the normal knee jerks were capable of reinforcement and those in hemiplegics were not, on either the "normal" or the affected side. Although this was the rule, a few subjects did not respond in this way. In these there was appreciable reinforcement on the unaffected side, and in this respect they resembled normal controls.

Paraplegia due to trauma (six cases): Of the six cases of traumatic paraplegia the values ranged from 30 to 7000 μv. (mean 1784 μv.). With reinforcement they varied between 30 and 6600 μv. (mean 1902 μv.). Thus, there was no significant reinforcement.

Paraplegia due to multiple sclerosis (11 cases): The values without reinforcement ranged between 160 and 10,000 μv., with a mean of 3644 μv. After reinforcement the range was 200 to 7600 μv. (mean 3631 μv.). Again, no significant reinforcement took place.

Latency of Reflex Response

The values obtained in normals, hemiplegics, and paraplegics were approximately 20 to 25 milliseconds and did not vary from one group to another. This corresponds to the normal range of latency for the knee jerk, as determined by Malcolm,[1] and also confirms Malcolm's observations that the latency time was not affected by upper motor neuron lesions. The latency time in both legs of the same individual was identical.

Wave Form of the Action Potential

The shape of the action potential was most commonly a symmetrical diphasic curve with rather sudden rises and falls and a rounded top (figure 2A). In some instances this wave was split or "M" shaped or "W" shaped (figure 2B). These

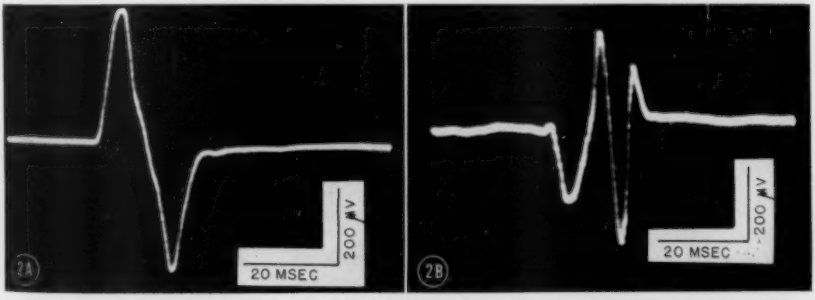

FIG. 2. *A.* Typical reflex potentials. Usual diphasic potential, in this case from a paretic subject. The latency time, from the start of sweep (on the left) to the take-off of the potential, is constant for the individual. *B.* Less common polyphasic potentials, in this case from a normal control. The latency time is longer than in 2*A* because the subject is taller.

polyphasic potentials occurred in normal as well as spastic limbs and could usually be transformed into the simpler wave forms by improving the electrode contact or by varying the angle of percussion. The shape of the wave was not found to be related to any pathologic condition.[2]

Duration of Action Potential

The duration of the action potential did not have any relationship to the disease condition and was more affected, as was the shape, by technical factors.

Effect of Mechanical Restraint

Preventing the leg from swinging by holding or strapping it did not affect any of the characteristics described above.

"After-Discharges"

The initial complex of many abnormal reflexes was followed by one or more additional complexes, some of them rhythmical. When visible clonus was present, they were synchronous with it. However, since they also occurred in normal subjects with hyperactive reflexes, their significance remains questionable. Sometimes reinforcement brought them out in normal subjects.

Variability

In general, the amplitude of the reflex potential in normal subjects varied considerably from one observation to the next (figure 3A), whereas in the spastic extremities all the reflexes were very much alike (figure 3B). The studies were repeated in a few subjects after several days or weeks. The absolute values obtained could not, of course, be reproduced, since they depended on technical factors, such as distance between the electrodes and skin resistance. However, the essential characteristics remained unchanged, that is, variability and reinforcement effects.

DISCUSSION

The essential finding in this study was that reinforcement did not increase the reflexes in the abnormal individuals, whereas reflexes of normal subjects increased significantly with the stimuli used. It was of particular interest that this lack of reinforcement also characterized the supposedly normal side in the hemiplegic cases. Three explanations of this phenomenon suggest themselves. 1) There may be bilateral cerebral disease. Although all of the patients with hemiplegia had vascular lesions, which are notoriously bilateral, full support of this explanation is not justified without autopsy material. 2) The spasticity of the abnormal side may act as a constant reinforcement for the unaffected extremities. We have little data bearing on this point. However, since the physiology of reinforcement is not known, this may simply be a restatement of certain facts in different words rather than an explanation of them. Also opposed to this theory is the fact that the uninvolved side of a few spastic hemiplegics responded like the normal. 3) At present the most plausible is the supposition that a lesion in one cerebral hemisphere results in dysfunction of other parts of the nervous system, including the opposite hemisphere.

An experimental approach to this problem was taken by Hirschberg and Nathanson,[3] who showed that the electrical patterns of muscle action were not normal on either side in the hemiplegic patient. They used multiple-channel electromyographic records of representative muscles in the lower extremity. After establishing the normal pattern of participation of various muscles in the different phases of gait, they found that the pattern of muscle activity in the

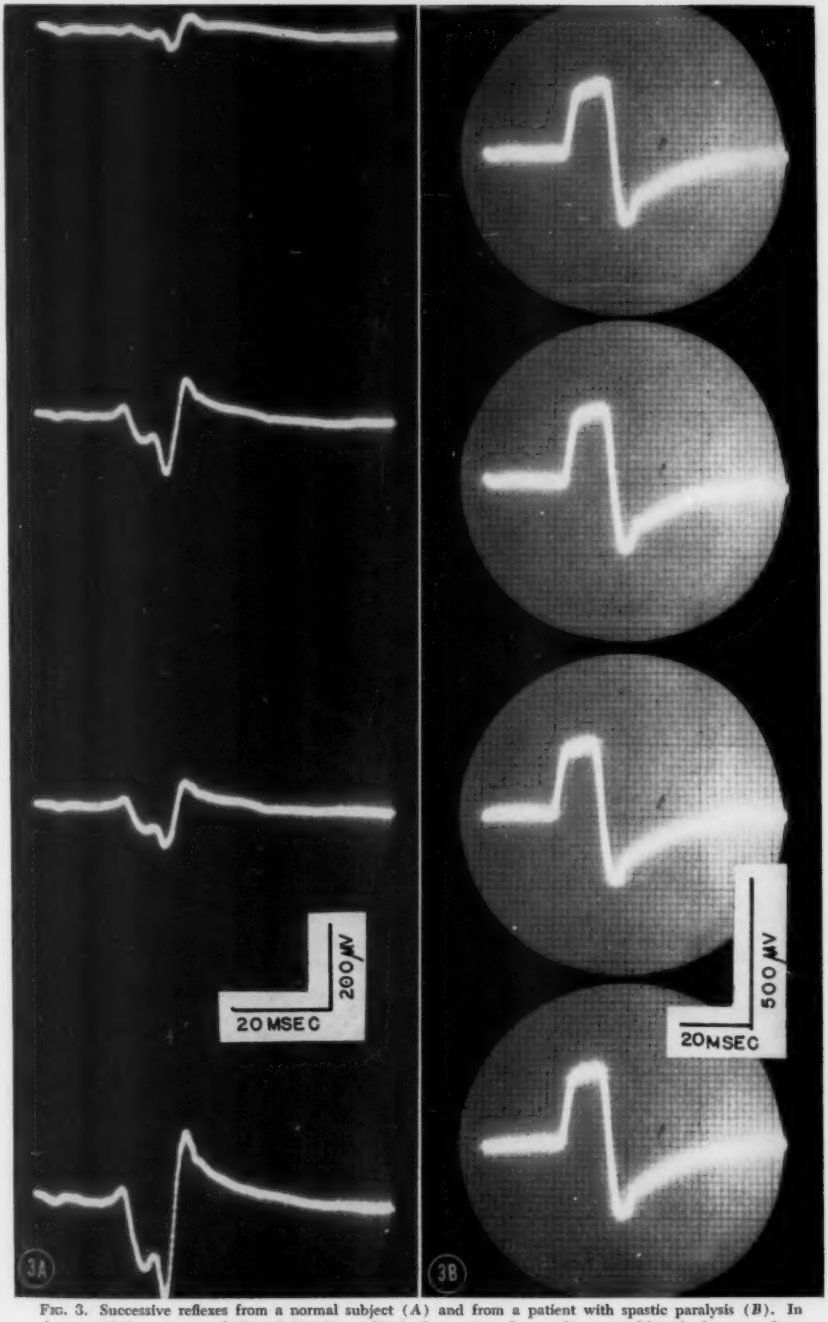

FIG. 3. Successive reflexes from a normal subject (*A*) and from a patient with spastic paralysis (*B*). In the normal there is a marked variation in amplitude from one reflex to the next, although the wave form remains the same. In the spastic limb successive potentials are almost identical, both in amplitude and configuration.

unaffected limb resembled that of the hemiparetic side more than it did that of a normal limb. In another experiment Wortis and co-workers[4] and Marks[5] took rapid-sequence photographs of the knee and measured the force of the foot on the ground during walking. They also discovered that both sides of the hemiplegic varied from the normal pattern.

The failure of the abnormal reflex to increase with reinforcement, which occurred in all the abnormal extremities whatever the cause, was at first believed to be merely a simple relationship. A reflex of high amplitude will not reinforce much, because most or all of the available muscle is already contracting and no further stimulus will be effective. This was not the case, since the reflexes on the unaffected side did not differ significantly from reflexes in the normal controls; reinforcement was nonetheless ineffective.

Another characteristic of the reflexes illustrates this point. The reflexes in normals were characterized by great variability from one reflex to the next, whereas in abnormals they varied much less or not at all. This suggests that the pattern of reflex organization induced by injury to the nervous system is a relatively rigid one, resistant to modifying influences. In the Jacksonian scheme, the nervous system is operating at a lower level of function and this level is less easily reached by stimuli operating chiefly at other levels. This change or reorganization of function which occurs in disease can be shown in the sensory and psychic spheres as well.

It is not known how reinforcement operates, nor do these experiments supply enough data for profitable speculation on this point. It is clear, however, from this and previous studies that there are numerous factors bearing upon the amplitude of the knee jerks in normal subjects, almost all of them impossible to measure. One of the most important is the psychologic state, as brought out by Lombard[6] 50 years ago. The hyperreflexia of some tense, anxious patients is well known. In this experiment it was possible to produce significant reinforcement by surprise, levity, distractions, and merely suggesting the effort of lifting a weight, as well as by actually lifting it. Whatever the mechanisms of reinforcement may be, and whichever of them were operating in our cases, they were much less effective in abnormal subjects than in normals.

SUMMARY

1. The knee jerks were measured by recording the electrical output of the quadriceps muscle after a standard stimulus. The reflex was studied at rest and under reinforcement in normal subjects, patients with spastic hemiplegia, and patients with spastic paraplegia due to trauma or multiple sclerosis.

2. The muscle stretch reflex in normal man behaves in a characteristic way under these conditions of testing; that is, it shows great variability from moment to moment and increases significantly with reinforcement.

3. The abnormal reflex is also characteristic in that it shows little variation from reflex to reflex and remains the same in spite of reinforcement.

4. In regard to the response to reinforcement, the reflexes of the uninvolved side in a significant number of patients with hemiplegia resembled those of the involved side rather than those of normal subjects. Some theoretical implica-

tions of this phenomenon are discussed.

5. This method of testing served to differentiate pathologic reflexes from the normally hyperactive ones.

The hammer or "reflex gun" used in this study was invented and is owned by Torricelli Creations, Inc., New York City.

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■ If we fix a thread to the tendon of a muscle of a frog and attach to this thread a weight, capable of entirely preventing the contraction of the muscle, which is fixed by its other extremity, we find that every time the muscle tends to contract, there is an excitation of the nerve lying upon it, and a contraction of the muscle to which this nerve is distributed. Hence it is not necessary for a muscle to contract in order to produce in nerves in contact with it a galvanic excitation. I repeat that it is sufficient that they *tend* to contract. Now, I have found that the greater is the resistance to the contraction of a muscle the greater is the galvanic excitation that it gives to nerves in contact with its tissue. On the contrary, if there is no resistance at all, as already shown by Professor Matteucci, after the section of the tendon, then the galvanic excitation of nerves in contact with the contracting muscle no longer exists.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System,* published in 1860.

Experimental Allergic Encephalomyelitis Following Administration of Homologous Brain Lipid Fractions

Norman P. Goldstein, M. D., Marian W. Kies, Ph.D., Alfred G. Karlson, Ph.D., Lawrence C. Kolb, M.D., Harold L. Mason, Ph.D. and George P. Sayre, M.D.

SINCE 1933 when Rivers, Sprunt, and Berry[1] first produced an encephalomyelitic condition in monkeys by injection of brain emulsion and an alcoholic brain extract, many attempts have been made to isolate and identify the substance in brain responsible for the lesions of the central nervous system. Various substances have been considered to be responsible for the encephalomyelitis, including lipids such as the phosphatides, lecithins, cephalins, and the cerebrosides, as well as lipid-free protein substances. Although it is generally agreed that a lipid-soluble material is involved, there has been wide divergence in results reported from different laboratories. For instance, Alvord[2,3] reported activity of an acetone-soluble fraction, whereas Kabat, Wolf, and Bezer[4,5] were unable to demonstrate activity of an acetone extract of brain. Ferraro, Roizin, and Cazzullo[6] observed slight activity of acetone-ether and ether extracts, while Olitsky and Yager[7] reported that an acetone-ether soluble fraction had no encephalitogenic potency. Koprowski and Jervis[8] reported that a methanol-chloroform extract of brain which they believed contained cerebrosides and sphingomyelin was capable of producing encephalomyelitis in experimental animals.

There are also reports of nonlipid preparations of brain having encephalitogenic activity. Bell, Wright, and Habel[9] demonstrated activity of a calcium acetate solution of brain after lyophilizing the brain and defatting it by extraction with benzene and ether. Ferraro and Roizin[10] also reported that a calcium acetate solution of defatted brain was active. Their procedure differed from Bell's in that acetone treatment of wet brain was used in place of the lyophilizer for drying the brain. Presumably the active "antigen" was a protein, soluble in the calcium acetate solution. Furthermore, Hottle, Nedzel, Wright, and Bell[11] demonstrated encephalitogenic activity of a water dialysate of lyophilized brain which had been defatted by extraction with benzene and ether, where-

The majority of the investigation here reported was performed while Dr. Goldstein was assistant to the staff in the section of neurology, Mayo Clinic.

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as Olitsky and Tal[12] were unable to reproduce this finding.

In an effort to clarify some of the questions regarding the nature of the material in brain responsible for the production of allergic encephalomyelitis, we undertook a study of this material. Our earlier work[13] confirmed the results of Olitsky and Tal[14] that the total lipid extract made according to the directions of Folch and associates[15] contained all of the activity. Waksman and co-workers[16,17] have also confirmed this observation. In the present report are summarized tests on other extracts, the results of which have some bearing on the chemical nature of the material.

METHODS AND MATERIALS

The production of the whole-brain antigen is essentially that described by Kabat, Wolf, and Bezer.[4] Nine parts of freshly removed guinea pig brain are mixed in a Waring blendor with 10 parts of 0.85 per cent solution of sodium chloride containing 0.5 per cent phenol, 10 parts of melted Aquaphor,* and 20 parts of liquid petrolatum containing 2.5 mg. of dead tubercle bacilli per milliliter. After the mixture is thoroughly blended, the resultant emulsion is heated at 60° C. for an hour. Finally, 1 ml. of this mixture is injected subcutaneously over the sternum of a male guinea pig weighing approximately 700 gm.

The groups of animals which were injected with the whole-brain mixture made up our control series. Eight different groups were injected with whole-brain mixture over the course of a year. Various lipid and protein fractions prepared from the brains of normal guinea pigs were substituted for the whole wet brain in amounts equivalent to their concentration in the standard weight of whole wet brain.

The experimental animals were observed for several weeks prior to injection to make sure no spontaneous encephalomyelitis would occur. Following injections, all animals were examined on alternate days for clinical evidence of disease in the central nervous system. When animals died during the experimental period, which varied from 46 to 66 days after injection, the brains and spinal cords were removed as soon as possible after death. The remaining animals were killed at the conclusion of the experimental period. Histologic examination of the brains and spinal cords of all animals was made without prior knowledge of which animals received whole brain and which animals received various extracts. Likewise, the period of clinical observation of the animals was controlled in so far as the observers were not cognizant of which animals received whole brain and which animals received the experimental fractions.

EXPERIMENTAL RESULTS

The results obtained with our control series[13] were published in an earlier paper. Of the total of 80 animals in this control group, 96 per cent demonstrated histologic changes typical of encephalomyelitis, while 86 per cent of the animals showed clinical evidence of disease of the central nervous system, mainly paralysis of the extremities. Although the mortality rate varied from 24 per cent to 75 per cent for the different groups of control animals, pathologic and clinical results were remarkably constant.

*Aquaphor is a hydrophilic emulsifier which contains 6 per cent cholesterol esters (from wool fat) and 94 per cent aliphatic hydrocarbons. (Supplied by Duke Laboratories, Stamford, Conn.)

TABLE 1
COMPARISON OF CALCIUM ACETATE PREPARATIONS WITH WHOLE BRAIN CONTROLS

Procedure	*Group*	*Animals*	*Histologic changes in C.N.S. Per Cent*	*Paralysis Per Cent*	*Mortality Per Cent*
Goldstein and associates [12]	Whole brain controls	80	96	86	54
Bell and associates [9]	Benzene fraction	10	0	0	0
	Ether fraction	10	0	0	0
	Calcium acetate fraction	10	0	0	0
	Final residue	10	30	40	30
Ferraro and Roizin [10]	Acetone fraction	6	0	0	0
	Benzene fraction	6	0	0	0
	Ether fraction*	0			
	Calcium acetate fraction	6	0	0	0
	Final residue	6	30	67	17

*Q.N.S. for assay in animals.

Under the same experimental conditions, we were unable to demonstrate any encephalitogenic activity in the calcium acetate extract of brain prepared according to the method of Bell, Wright, and Habel[9] or a similar fraction prepared according to Ferraro and Roizin.[10]

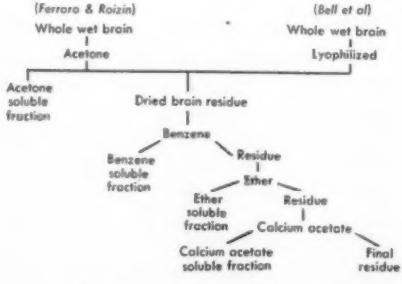

FIG. 1. Preparation of calcium acetate protein fractions.

The preparations are shown schematically in figure 1. Except for the first step, the two procedures were essentially identical. All of the fractions obtained were tested except the ether-soluble extract of acetone-dried brain. There was too small an amount of this fraction to test. Only the final residues showed encephalitogenic activity (table 1).

The dialysate of lyophilized, defatted brain, prepared (figure 2) according to Hottle, Nedzel, Wright, and Bell,[11] yielded three fractions for testing of activity: the dialysate; the water-soluble, nondialyzable fraction inside the dialysis bag; and the water-insoluble residue. Of these, only the water-insoluble residue

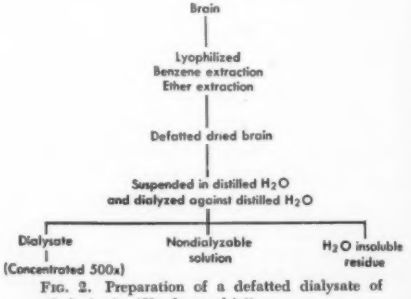

FIG. 2. Preparation of a defatted dialysate of whole brain (Hottle et al.).[11]

TABLE 2

COMPARISON OF DIALYZED DEFATTED BRAIN AND DIALYSATE (HOTTLE ET AL.) WITH WHOLE BRAIN CONTROLS

Group	Animals	Histologic changes in C.N.S. Per Cent	Paralysis Per Cent	Mortality Per Cent
Whole brain controls	80	96	86	54
Dialysate*	10	0	0	0
Dialysate (concentrated 500x)	10	0	0	0
Nondialyzable H_2O soluble material	10	0	0	0
H_2O insoluble residue Nondialyzable H_2O soluble material	10	40	50	10

*This dialysate contained less than the standard amount of brain extract.

proved to be active (table 2). Although Hottle and associates[11] found activity in the dialysate, we were unable to confirm this observation even after the dialysate had been concentrated 500-fold.

The chloroform, pyridine, acetone, and petroleum ether fractions described in figure 3 were prepared by triple extraction with each solvent, each individual extraction being carried on for 24 hours at 0° C. The ratio of the brain to the solvent was 1:20 (weight : volume). After extraction, the solvent was removed by vacuum distillation; the material was aerated to remove the last traces of the solvent and then dried in vacuum over sulfuric acid. Only the chloroform-soluble material possessed encephalitogenic activity (table 3). It should be noted that the residue left after extraction with chloroform was just as potent as the chloroform-soluble fraction. None of the other extracts caused encephalomyelitis in the experimental animals.

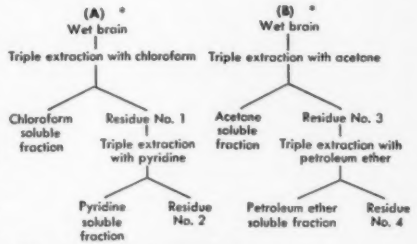

FIG. 3. Extraction of fresh brain with organic solvents.

DISCUSSION AND SUMMARY

Various procedures for making encephalitogenic extracts of brain material have

TABLE 3

COMPARISON OF LIPID FRACTIONS AND RESIDUES WITH WHOLE BRAIN CONTROLS

Group	Animals	Histologic changes in C.N.S. Per Cent	Paralysis Per Cent	Mortality Per Cent
(A) Whole brain controls	80	96	86	54
Chloroform extract	16	100	100	81
Residue No. 1	16	75	63	44
Pyridine extract	6	0	0	0
Residue No. 2	6	67	67	50
(B) Acetone extract	6	17	0	0
Residue No. 3	6	0	17	17
Petroleum ether extract	6	33*	0	0
Residue No. 4	6	33*	17	17

*Questionable changes in brain and none in spinal cord.

been repeated and the extracts tested under carefully controlled conditions. Our results fail to confirm previous reports that a nonlipid substance is capable of inducing allergic encephalomyelitis in experimental animals. We could not demonstrate encephalitogenic activity in either a calcium acetate extract or a water dialysate of defatted brain.

Of the lipid solvents tested, only chloroform yielded an extract with marked encephalitogenic activity. However, this solvent leaves a residue still possessing considerable activity. Since it has been repeatedly shown that chloroform-methanol mixtures completely remove the activity from whole brain, it is postulated that there are at least two "antigens" present, one of which is chloroform-soluble and the other insoluble in chloroform, but soluble in a chloroform-methanol mixture. Further work is at present being carried out on the isolation and characterization of these agents.

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Systemic Absorption and Urinary Excretion of RISA from Subarachnoid Space

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THIS IS a preliminary report of a study on systemic absorption and clearance of radioactive iodinated human serum albumin (RISA) injected intrathecally in the lumbar region. It is also an investigation of the rate of diffusion of RISA in the cerebrospinal fluid along the neural axis.

When RISA is injected intravenously, its diffusion into various fluid compartments of the body including the cerebrospinal fluid, its metabolic turnover, and its biologic half-life have been documented.[1,2] Furthermore, various substances, radioactive or otherwise, have also been studied with respect to the rate of diffusion into cerebrospinal fluid from the systemic circulation. However, there have been few reports on the "reverse traffic" of substances from the cerebrospinal fluid to the blood stream. It is hoped to find an optimum interval for performing isotope ventriculography with scanning scintillation apparatus by learning the diffusion rate of RISA in the cerebrospinal fluid and absorption and clearance rates from the blood.

METHOD

Adult patients are selected at random, some bedridden but others ambulatory with no restriction placed on their activities. With the patient in a lateral decubitus position, a spinal puncture is made at L_4-L_5 interspace. Then approximately 100 microcuries of RISA diluted in 2 cc. of normal saline solution is injected. The injection is made slowly with the bevel of the spinal needle pointed cephalad. The patient is immediately turned to a prone position. The distance from the site of puncture to the base of the skull overlying the cisterna magna is measured. This length is divided into thirds to provide four equidistant points as shown in figure 1. The upper level of the coccyx is marked point 5 and the midpoint between the parietal eminences is marked P. Using a bismuth cathode G-M tube and a Berkely scaler, the activity in the spinal cord under each point is measured at 15 minute intervals for an hour, then at hourly intervals for four hours, and finally at four-hour intervals for three days. An area arbitrarily chosen

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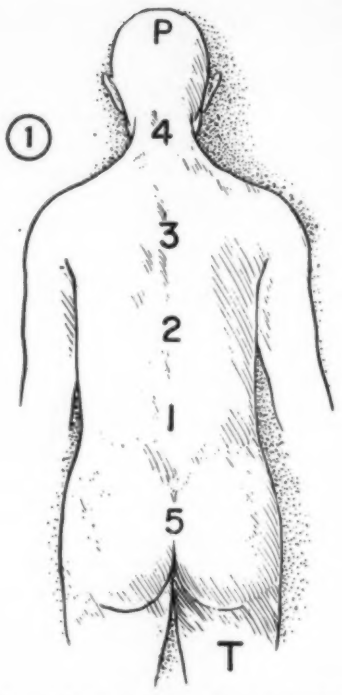

FIG. 1. Points along the spinal column studied after injection of RISA.

over the midthigh is also measured as the background. Following the intrathecal injection of RISA, daily blood and 24-hour urine specimens are collected. The activity in each specimen is measured by counting 2 cc. of the specimen in a special vial in the well-scintillation counter.

RESULTS

A total of eight patients were studied. For the purpose of presentation the results will be discussed under the following headings:

Intrathecal diffusion along the neural axis: A typical diffusion curve is shown in figure 2. After introduction of the tracer material, diffusion takes place immediately both cephalad and caudad. Neither the cisterna magna nor the parietal area shows a significant accumulation of activity during the first hour. At this time the cisterna magna activity level increases. At the end of the second hour the parietal activity level also begins to rise. The rate of increase in the cisterna magna and the parietal area exceeds that of the upper thoracic region. This is probably due to a greater cerebrospinal fluid volume in the cisterna magna and the parietal region. After the eighth hour, activity levels over each point change very slowly, but equilibrium is not established until almost the twentieth hour following injection. Approximately 24 hours postinjection the activity in the thigh reaches its peak and then decreases gradually paralleling the decrease of all the areas.

Systemic absorption: This is shown in figure 3. Only daily specimens were studied. No attempt was made to measure multiple samples in the first 24 hours following intrathecal injection of the tracer material. The peak of activity is reached in about 40 hours. From then on, there is a gradual disappearance of RISA from the blood stream. It can be assumed from this study that the exchange of RISA between cerebrospinal fluid and the blood is in equilibrium at about 40 hours following intrathecal administration. This is in contrast to equilibrium at 20 to 24 hours when RISA is injected intravenously.[1]

Urinary excretion: Figure 4 shows the urinary excretion of RISA as expressed in percentages of the total activity injected. The peak of excretion occurs on the second day after injection. This corresponds to the peak of blood activity.

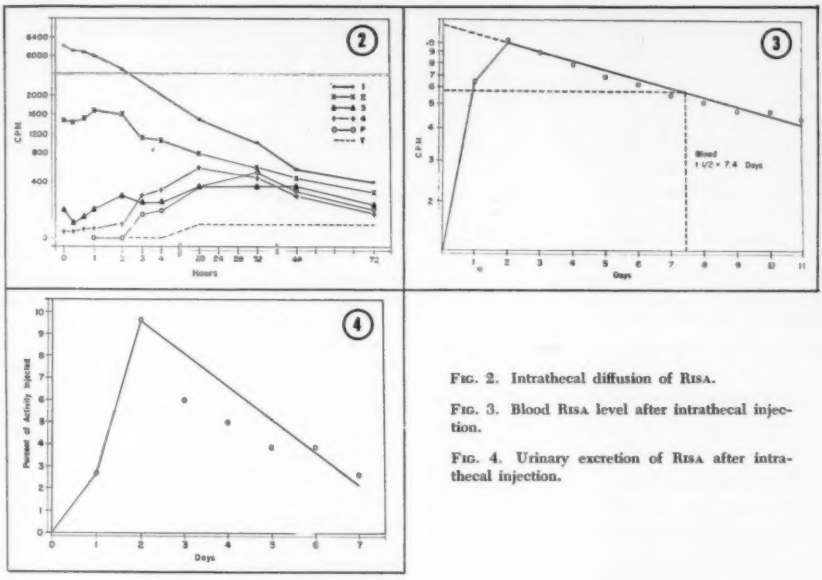

FIG. 2. Intrathecal diffusion of RISA.

FIG. 3. Blood RISA level after intrathecal injection.

FIG. 4. Urinary excretion of RISA after intrathecal injection.

DISCUSSION

There are several interesting points that need further discussion. First, it has been shown by this study that diffusion of a substance in the cerebrospinal fluid along the neural axis is a slow process. It takes at least 20 to 24 hours to reach an equilibrium in all the cerebrospinal fluid compartments. Secondly, when RISA is injected intrathecally, cerebrospinal fluid-blood equilibrium is not established until some 40 to 48 hours. This almost doubles the equilibrium time after intravenous RISA injection. There are at least two reasons for this finding. When RISA is injected intravenously, mixing is complete in several minutes, whereas it takes 20 hours to accomplish the same in the cerebrospinal fluid. Obviously there is a lag in exchange along the entire neural axis before complete mixing is established. Hence the delay in establishing the cerebrospinal fluid-blood equilibrium. Similarly, the plasma biologic half-life of RISA when introduced intrathecally is up to 7.5 days compared to the 6.3 days reported by Fishman (figure 3).

It appears that the optimum interval for isotope ventriculographic study is approximately 24 hours after intrathecal injection of RISA. This is when the cerebrospinal fluid activity is highest as compared to a rising blood activity.

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Clinical Study of Craniopharyngiomas Occuring in Persons Over 40

Iris Fletcher Norstrand, M.D.

THE MAJORITY of craniopharyngiomas occur in childhood or young adult life, and at this age usually present no problem in diagnosis. Rathke pouch tumors occurring in older persons, however, do not have a typical clinical picture and often are unsuspected.

A case of suprasellar cyst in a man of 42 prompted a study of other cases first manifesting symptoms after the age of 40. The records of all cases of craniopharyngioma admitted to the New York Neurological Institute between 1932 and 1949 were studied. Of a total of 83 cases of hypophyseal duct tumors admitted during these years, only five histologically verified cases occurred in individuals over 40. A greater number were diagnosed as craniopharyngiomas, but since this was never confirmed by operation or autopsy these cases are not included.

CASE REPORTS

Case 1.—A 41 year old married Italian plater was admitted to the neurology clinic of the Long Island College Hospital on April 8, 1948. He had been well until two months before admission, when he began to have ocular symptoms consisting of slight pain, a sensation of having a foreign body, dimness of vision, and "flickering" in the right eye. Since February 1948 he had been having brief attacks in which he had a sudden sensation of "ants crawling," beginning in the outer aspect of the right foot and travelling up the right lower extremity to the epigastrium, accompanied by nausea and a feeling of panic. The dysesthesias then continued up the right chest and the back of the neck, omitting the right upper extremity and face. The whole episode lasted only a few seconds and was not accompanied by any motor manifestations or disturbance of consciousness. The patient stated that he was always terrified during these spells, which occurred anywhere from two or three times a day to once a week. At the initial examination there was no complaint of headache and there were no other symptoms. Past history and family history were irrelevant. He had served in the air corps from 1942 to 1945, and had been married for six months.

Admission examination showed a healthy-looking, rather heavy-set, intelligent male. Temperature, pulse, and respirations were normal. Blood pressure was 120/75. Heart, lungs, and abdomen were normal. There was no suggestion of an endocrinopathy. Gait and station were normal. Cranial nerves were intact, except for the following: Visual acuity: OD-20/100; OS-20/30. Pupils were regular and equal. The right pupil did not react to light or accommodation, but reacted to light consensually. Fundi were normal, except for questionable pallor of the right disk. Extraocular movements were normal. There was a horizontal nystagmus on left lateral gaze. Motor power and sensation were intact. Deep reflexes were equal and hyperactive throughout. The left abdominal reflex was diminished. There were no other abnormal reflexes.

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Although a definite diagnosis was not possible on the basis of the clinical findings, an intracranial tumor or multiple sclerosis were considered and a complete work-up was ordered. For various reasons, however, the patient did not have the studies done, and failed to return until a year later (June 2, 1949), when he again complained of continued impairment of vision and slight pain in the right eye and the right-sided dysesthesias as described above. Additional symptoms were as follows: Since October 1948 he had noted frequent shaking of both lower extremities, an occasional heavy feeling in the left lower extremity, and slight weakness in his left hand. He had also had frequent mild headaches, beginning in the back of the neck on both sides, and radiating forward to both frontal regions, occurring mostly in the morning and relieved by Bromo-seltzer. There had been some nausea and vomiting in the past few months. Loss of libido had been noticed for the past six months. There had been a weight loss of 11 pounds in the past year. There was no polyuria, polydipsia, polyphagia, or somnolence.

On neurologic examination the patient appeared somewhat euphoric. There was weakness and marked spasticity of the left upper extremity and slight spasticity of both lower extremities without demonstrable weakness. There was a left lower facial weakness. Deep reflexes were hyperactive throughout, with left preponderance in the upper extremities and equal reflexes in the lower extremities. Left abdominal reflex was diminished. There was an equivocal Babinski bilaterally. Sensation was intact. Smell was diminished on the right. Pupils were regular and equal; the right pupil did not react to light or accommodation, but reacted to light consensually. Fundi were normal. There was a horizontal nystagmus on left lateral gaze. Visual fields showed a left homonymous hemianopsia, with sparing of the maculae. Visual acuity: right eye, 2/200; left eye, 20/40.

Roentgenograms of the skull showed erosion of the right anterior clinoid, which was more strongly pointed than the left. There was calcification in the region of the sella, mainly to the right of the midline. Pineal shadow appeared to be in the midline. The anterior, middle, and posterior fossae were normal. The right optic foramen was normal. The left optic foramen was not well visualized. Urine, blood count, and serology were negative.

The electroencephalogram (monopolar and bipolar recordings) showed continuous irregular activity, particularly over the right parietal zone where considerable six to eight cycle per second activity showing distorted wave forms was observed. With the use of temporal leads, an irregular pattern appeared most pronounced in the temporal and parietal zones. Hyperventilation produced no change in the pattern. Abnormal activity over the right temporal and parietal areas suggested a temporoparietal focus on the right, that is, an expanding lesion situated deeply and fairly extensively in the right parietotemporal region.

Immediate hospitalization was ordered but refused at this time. The patient grew progressively worse, developing unsteadiness of gait, severe headaches, slight weakness of the left lower extremity, and episodes of shaking of both lower extremities.

Examination on July 21, 1950 disclosed a cheerful, mentally alert man, who looked surprisingly well. Gait was slightly unsteady. Smell was diminished on the right. Pupils were regular and equal, the right pupil did not react to light or accommodation. Funduscopic examination showed blurring of both nerveheads, with 2 diopters of papilledema on the right and 1 diopter on the left. There were flame-shaped hemorrhages in both retinas, more on the right. There was a left homonymous hemianopsia, with sparing of the maculas. There was a horizontal nystagmus on left lateral gaze. There was a left lower facial weakness and a left hemiparesis, much more marked in the left arm which was markedly spastic. Deep reflexes were hyperactive, with preponderance in the left upper and lower extremities. Left abdominal reflexes was diminished. There was a left Babinski reflex.

The patient was finally admitted to the Long Island College Hospital on August 1, 1949. The day before admission he had a tonic seizure, which consisted of loss of consciousness and extension and rigidity of all four extremities for several minutes. At hospital admission his condition seemed excellent, with normal vital signs and no evidence of intracranial decompensation. The next day an arteriogram was done under Pentothal anesthesia, revealing a huge suprasellar mass.

Operation: Following arteriography, the pa-

tient remained stuporous and lapsed into deep coma 24 hours later, with a systolic blood pressure of 180 mm. An emergency craniotomy was done, with turning of a right frontal bone flap. The dura mater was under extreme tension and remained so despite ventricular tap. On opening the dura mater, considerable herniation of the brain was observed. The gyri were most flattened in the temporal region. Incision was made into the temporal lobe and, just beneath the surface, a cyst was encountered containing approximately 50 or 75 cc. of brown fluid which appeared grossly to contain cholesterin crystals. The inside of the cyst was investigated, and it was seen to occupy practically all of the temporal lobe and to pass medially almost to the midline. The tissue at the most medial extreme of the cyst was very firm. The cyst was lined by a thin, slimy brown membrane. As evacuation of the cyst had not significantly reduced the herniation of the brain, a considerable amount of the temporal lobe was extirpated. Since the herniation was still not satisfactorily reduced, the anterior two-thirds of the frontal lobe was extirpated. In this latter procedure the cyst was not encountered, indicating that it did not extend into the anterior portion of the frontal lobe. The patient failed to rally, and expired eight hours postoperatively.

Histologic study of specimen: The specimen, which was a portion of the cyst wall, consisted of two pieces of finely-lobulated, irregularly-shaped, relatively firm brown tissue, approximately equal in size, and measuring 11x6x3 mm. It was lined for the most part by well-differentiated, stratified squamous epithelium, in a few areas showing a tendency toward stratified columnar epithelium. The stroma was relatively scanty, delicate, and vascular. Sediment from the cyst fluid consisted almost entirely of red blood cells, with a few scattered, large mononuclear cells, and rare masses resembling cholesterol crystals.

Case 2.—A 43 year old married instrument maker was first admitted to the N. Y. Neurological Institute on January 29, 1946, with a history of headaches occurring every three or four days, periods of somnolence and confusion since July 1945, and loss of libido since September 1945. There was a history of mild head trauma in November 1945. The patient had married at the age of 37, and had no children.

On admission examination the patient appeared confused. Blood pressure was 120/82. Gait and station could not be tested. There was a slight tremor of both hands and slight weakness of the right hand grip. There was questionable dysdiadokokinesis on the right. The deep reflexes were slightly increased in the right upper and lower extremities. Abdominal reflexes were diminished on the right. There was a positive Hoffman and an equivocal Babinski on the right. Sensation was probably intact. Cranial nerves were normal except for the following: The right pupil was larger than the left. Both reacted well to light and accommodation. Extraocular movements were normal. Palpebral fissures were equal. Fundoscopic examination showed slight temporal pallor of the right disk. Visual fields were not done because of lack of cooperation. A Roentgenogram of the skull was considered normal, except for a little calcification over the upper part of the sella considered to be a calcified interclinoid ligament. The pineal was not visible. The electroencephalogram showed long runs of medium voltage, 3 per sec., more marked on the left. Bipolar leads showed focal signs over both frontal and temporal areas, left more than the right, indicating a huge left-sided focus with a "mirror" focus on the right. A pneumoencephalogram was done, but was unsatisfactory. Urinalysis, serology, blood studies, and sedimentation rate were negative. Spinal fluid was under normal pressure, with a total protein of 46 mg. per cent and 5 leukocytes. During his hospital stay the patient improved a great deal, so that when discharged on February 14, 1946 he was asymptomatic and had a normal neurologic status, except for apprehension and generalized fine tremor. No diagnosis was offered at this time. An electroencephalogram on discharge showed that the record had improved markedly, although the focal signs still persisted in the left temporal area. Fundi, visual acuity, and visual fields were normal.

The patient was symptom-free for one and one-half weeks after leaving the hospital. He then developed weakness of the legs, described as "buckling of the knees," and gradually became apathetic, disoriented, and occasionally incontinent of urine. On March 13, 1946, one week before the second hospital admission, he had a seizure characterized by weakness in both lower extremities, followed by unconsciousness,

with rigidity of the left hand, and rigidity and extension of both lower extremities. After this attack, he remained stuporous for two hours and exhibited a bradycardia (54-58 per minute).

Examination showed a quiet, apathetic, and uncooperative man whose blood pressure was 132/88. Neurologic examination was negative, except that the right pupil was larger than the left. Fundi were normal. Spinal fluid was under normal pressure, with total protein of 56 mg. per cent and two white cells per cu. mm. Ophthalmologic examination on March 20 was as follows: Visual acuity—OD-20/70-2; OS-20/30-2. The optic fundi were unusual. The temporal halves of the disks were still pale and temporal margins quite sharp and suggestive of primary optic atrophy, whereas the nasal halves were injected, edematous, veins engorged and tortuous, and there were hemorrhages on the nasal half of the retina in the left eye.

A ventriculogram showed that both lateral ventricles were dilated and displaced to the right. The third ventricle failed to fill.

Operation: On March 25 a right frontal Frazier osteoplastic flap was turned under local and Pentothal anesthesia. A craniopharyngioma protruding into the third ventricle was found. This was evacuated, and the wall of the cyst widely opened into the third ventricle.

Histologic examination revealed an adamantinoma of craniobuccal origin. Except for the development of a left spastic hemiparesis, which gradually cleared completely, this patient did well postoperatively. He felt well and was considering going back to work until December 1946, when he became dull and suffered five generalized convulsions in the next two months. Examination at this time disclosed a slightly unsteady gait, mild ataxia in the upper extremities, generalized hyperreflexia, more marked in the left extremities, with a positive Hoffman and Babinski on the left. Fundi showed a primary optic atrophy. Visual fields were normal. The patient slowly regressed, becoming obese and mildly lethargic. Six months before his death, visual fields showed a left homonymous hemianopsia. He died on July 15, 1949. Details of death are not known.

Case 3.—A 51 year old German-Jewish housewife, who was admitted to the N.Y. Neurological Institute on February 3, 1949, developed polydipsia rather acutely in July 1947, one and one-half years before admission. For a period of 15 months she had consumed 2½ to 3 quarts of water daily, with polyuria. There was no polyphagia. In July 1948 impairment of vision in both eyes, loss of color vision, anorexia, and a weight loss of 40 pounds occurred. In August 1948 fatigue and weakness, frequent drowsiness, decrease in libido, and mental depression were noted. In October 1948 frontal headaches, aggravated by movements of the head or coughing or straining, were first experienced. Menopause had begun at the age of 37. Admission examination showed a drowsy patient who showed evidence of recent weight loss. The skin was dry and scaly. There was no axillary or pubic hair. Blood pressure was 100/50, pulse 60. Gait was slightly unsteady, and the patient walked with small steps. Right arm swing was reduced. Succession movements were poorly performed with the right upper, and there was a slight drifting of the right upper extremity. There was weakness of the right upper and lower extremities, more marked distally. Headache was elicited on rapid passive movements of the head. Abdominal reflexes were absent. Tendon reflexes were active and equal. Both ankle jerks were absent. There was a questionable Babinski on the right, and a highly doubtful one on the left. Extraocular movements were normal. There was temporal pallor of both disks, left more than right. Visual field studies revealed a bitemporal hemianopsia (with hardly any sparing of the maculae). Visual acuity was OS-20/100; OD-20/100.

Laboratory studies of urine and serology were negative. The basal metabolic rate was minus 29. Blood count revealed a moderate secondary anemia. Serum cholesterol was 330 mg. per cent; sedimentation rate 50 mm/hr. Spinal fluid showed normal pressure, with a total protein of 56 mg. per cent and two white cells. Roentgenogram of the skull was negative, except for evidence of a right ethmoid sinusitis. Roentgenogram of the optic foramina was normal. The electroencephalogram was normal. Psychometric examination showed an intelligence quotient of 79, with evidence of deterioration.

The pneumoencephalogram revealed a large suprasellar tumor occupying the position of the hypothalamus and extending forward and backward from this area to elevate the floor of the anterior horns and posterior part of the third ventricle.

Operation: A right frontal flap was turned, and a cyst evacuated from the suprasellar region. Biopsy taken proved to be an adamantinoma. Postoperatively the patient improved in regard to visual acuity, general physical strength, and appetite.

Case 4.—A 53 year old white female was admitted to the N. Y. Neurological Institute on March 4, 1934, and died on March 26, 1934. In 1929 she developed easy fatigability and difficulty in walking, with a tendency to festinate. Shortly thereafter, right temporal headaches, which she had had on and off all her life, became worse and were associated with vomiting. Early in 1931 vision began to fail; she experienced episodes of confusion and was often somnolent. In the fall of 1932 there was polydipsia and polyphagia, with a weight gain of 30 pounds. Ten months prior to admission, urinary and fecal incontinence developed.

Examination revealed an elderly, obese woman, who was uncooperative and mumbled unintelligently. There was pronounced dysarthria. There was slight nuchal rigidity. There was generalized overactivity of the deep reflexes. Reflexes in the lower extremities were very active, with permanent clonus of the left suprapatellar jerk and transient clonus of the right. There was a right Babinski and confirmatories, and an equivocal left Babinski. Abdominal reflexes were absent bilaterally. There was a left internal strabismus. Pupils were regular and equal, but reacted sluggishly to light. There was pallor of both optic disks, with narrowing of the vessels. Cranial nerves were otherwise intact. Laboratory studies gave negative blood count, urinalysis and serology findings. Spinal fluid was under normal pressure, and contained 18 lymphocytes and 54 red cells. Total protein was 75 mg. per cent, 1 plus globulin. Roentgenograms of the skull showed a faint collection of calcium flecks directly over the sella and extending posterior to it.

Pneumoencephalogram, after the introduction of 85 cc. of air, showed that both lateral ventricles were moderately and symmetrically dilated. The ventricles were in normal position. The third ventricle was displaced upward. Only the superior part of the third ventricle was visualized. The inferior portion of the left frontal horn had a concavity inferiorly, probably due to pressure from the tumor.

Operation: On March 24 a right transfrontal craniotomy was done. Exploration of the region of the chiasm revealed no evidence of tumor, but a right transcortical incision into the right lateral ventricle disclosed a bulging cyst wall on the floor of this ventricle, yielding a fluid containing cholesterin crystals. The patient failed to rally postoperatively. Histologic examination showed the tumor to be a typical craniobuccal cyst.

Case 5.—A 42 year old chauffeur was admitted to the N. Y. Neurological Institute on May 25, 1944, complaining of nausea and vomiting and poor vision in the left eye. He had had no serious illnesses and was well until July 1941, when, following a head injury without loss of consciousness, he began to have severe pounding headaches involving the entire head and often associated with dizziness. In November 1941 he had a number of episodes of elevated temperature (101°-102°), accompanied by chilly sensations. These attacks lasted about three days, and occurred every two or three months. No further symptoms developed until April 1944, at which time he became nauseated, sleepy, and slightly disoriented during one of the headaches. Two days later, he had several chills, vomited profusely, had a fever of 103°, and was confused. He was admitted to Grasslands Hospital for two and one-half weeks in April 1944, where a pneumoencephalogram and other tests were performed; the results of these studies are not known. Following discharge, he was unable to return to work and complained of almost continuous headache, drowsiness, polyphagia, blurring of vision in the left eye, impairment of memory, and difficulty in the use of the left lower extremity. Shortly before admission to Neurological Institute, he gained about 15 lb. Two days before entry he had a severe bout of headache, began to vomit, became drowsy, and had a temperature of 103° with chills.

Examination showed a well-developed, well-nourished, drowsy adult male, who was confused and disoriented as to time and place. There was normal hair distribution, and no suggestion of an endocrinopathy. Temperature was 99.6°, pulse 60, respirations 20. Blood pressure was 180/100 (minimum during stay was 148/90). Heart, lungs, and abdomen were negative. On neurologic examination, there were no objective findings except for inability to see out of the left temporal field.

Laboratory findings for blood count, serology, sedimentation rate, blood sugar, and nonprotein nitrogen were all normal. The urine showed 1 plus albumin. Spinal fluid was under normal pressure with protein 48 mg. per cent, later rising to 100 mg. per cent; and six to 13 white cells per cu. mm. The fluid was normal otherwise. A blood culture was negative. The electrocardiogram showed slight left axis deviation. Roentgenograms of chest, skull, and optic foramina were normal. Since the nature of this illness was not clear, a pneumoencephalogram was done on June 6, 1944 to rule out a brain tumor. Films showed a large filling defect in the anteroinferior part of the third ventricle. The lateral ventricles were symmetrically dilated.

Operation: On June 14, a craniotomy was done under local anesthesia, and a right frontotemporal flap turned. The corpus callosum was split, exposing the right lateral ventricle and lamina terminalis, but no tumor was visualized. Following the operation, patient's temperature remained elevated (102°-104°), with a corresponding gradual rise in respiratory and pulse rate and the development of paralysis of left upper and lower extremities. He became comatose and died on the fifth postoperative day.

Autopsy: The brain weighed 1,260 gm. The cerebral hemispheres were approximately symmetrical. There was flattening of the gyri and sulci throughout. There were petechial hemorrhages into the leptomeninges and underlying cortex in the posterior portion of the right superior frontal gyrus. The leptomeningeal vessels were somewhat congested. A cystic tumor was found at the base of the brain, in the hypothalamic region. It was coarsely lobulated, encapsulated, light yellow, and firm. It measured approximately 3 to 5 cm. in cephalocaudad direction, 1.5 cm. dorsocentrally, and 2 cm. from side to side. At a number of points cysts could be seen showing through the capsule of the tumor. These were oval and appeared to be filled by a translucent greyish fluid. The optic chiasm and nerves were displaced dorsally and anteriorly, and the left side of the chiasm and medial half of the left optic nerve were considerably flattened. The chiasm and optic nerve were rotated so that the left optic nerve lay further anteriorly than the right. Histologically the tumor was a typical craniobuccal adamantinoma.

Case 6.—A 58 year old dancing teacher and housewife was admitted to the N.Y. Neurological Institute on June 17, 1946, with a history of polyphagia, increasing weight gain for two years before admission, weakness of both legs, staggering gait, and marked distaste for the odor of cooking fats for six months before admission. In addition, the patient had suffered from episodes of urinary incontinence, frequency, and nocturia for two years before admission. At the time of hospitalization there was no complaint of headache, nausea, or vomiting. For some time she had noted an occasional sensation of a "grey veil over both eyes." She married at 24 and was the mother of two children. There had been two or three miscarriages.

The patient was a very cooperative and intelligent woman of thick, athletic habitus. Heart, lungs, and abdomen were negative. Gait was normal. The patient stood better on the right heel than the left. Motor power and sensation were intact. There were no cerebellar signs. Deep reflexes were equal and hyperactive in the upper extremities and moderately active and equal in the lower extremities. Abdominal reflexes were absent bilaterally. There were no abnormal reflexes. Cranial nerves were intact. (Pupils were regular, equal, and reacted well to light and accommodation.) Fundi were normal. Extraocular movements were normal.

Laboratory findings for blood and urine were negative. Blood count revealed a secondary anemia. Spinal fluid was under normal pressure with a total protein of 50 mg. per cent and two white cells. A roentgenogram of the skull showed that the sella was normal in size and contour, but demonstrated slight demineralization of the dorsum. The pineal was displaced ½ mm. to the left of the midline, but this was not considered significant as its position appeared normal stereoscopically.

No diagnosis was made and the patient was discharged, only to be readmitted on July 19, complaining of increasing unsteadiness of gait, failing vision, difficulty in seeing to the left, recent disorientation for time and place, impairment of memory, postural fronto-occipital headaches, dysphagia for liquids (accompanied by coughing and marked congestion of the face), urinary incontinence, somnolence, tremor of both upper extremities increased on performance of purposeful movements, and the development of an external squint in both eyes.

The patient was drowsy and unable to walk. There was inability to perform the finger-to-nose test. Motor power and sensation were intact. Reflexes were equal and moderately active in the arms and equal and quite active in the legs. Abdominal reflexes were absent on both sides. Bilateral Babinski responses were elicited. Visual acuity was OD-20/70; OS-20/70. Visual fields could not be tested because of the patient's mental state. Pupils were regular, equal, and reacted sluggishly to light and accommodation. There was a bilateral external strabismus. Palpebral fissures were normal. The fundi showed right nasal blurring, and blurring at poles and nasal margins on the left.

Ventriculography showed that the lateral ventricles were considerably dilated, but there was no filling defect or abnormality of position. A small amount of gas was visible in the anterior portion of the third ventricle, but the remainder of the third ventricle failed to fill. The floor of the lateral ventricles was slightly elevated in the region of and a little behind the foramina of Monro. There was an impression of an expanding lesion in the third ventricle, probably a colloid cyst. Ventricular fluid contained protein 10 mg. per cent, with four white cells. The electroencephalogram was abnormal, with suggestive right-sided focus.

Operation: A right frontoparietal osteoplastic flap was turned under local anesthesia on July 20. The foramen of Monro was opened widely, and a bluish, discolored membrane was observed just within the foramen, occupying the anterior portion of the third ventricle. Aspiration revealed a thin cloudy fluid. The main attachment of the cyst was in the anterior wall of the third ventricle. The cyst wall was apparently completely removed. Except for transient polydipsia postoperatively, the patient was much improved; she lost much of her excessive weight and appetite, and had a better gait and better vision. She was doing well until October 1947 when she experienced pain over the right supraorbital region. In November 1947 she began having spells characterized by an aura of dizziness, a feeling of coldness, and then complete collapse, with unresponsiveness for 20 minutes, followed by transient ptosis of the right eyelid. In February 1948 there was diminution of vision again, and a weight gain of 10 pounds.

Examination showed a blood pressure of 120/76. Gait and station, motor power, and sensation were normal. Deep reflexes were increased in the left upper and lower extremities. Abdominal reflexes were present and equal. There were no abnormal reflexes. Visual acuity was OD-20/100; OS-20/50. The fundi showed blurred papillae, with 1 diopter of papilledema. Visual fields were normal. A roentgenogram of the skull showed a change in the appearance of the sella since the first operation, consisting of marked atrophy of the posterior clinoids and dorsum. The floor of the sella was depressed and the cortical margin of the floor was demineralized. The pineal was in the midline. An electroencephalogram showed a clearcut right temporoparietal focus extending forward to the motor area.

Operation 2: The old flap was reelevated on March 23, 1948 and a transfrontal approach to the third ventricle made, with partial removal of the neoplasm in the anterior part of the third ventricle. The tumor filled and distended the anterior part of the ventricle to a considerable extent, but did not extend to occlude the foramina. The tumor was identified histologically as of craniobuccal origin. Following operation the patient made a satisfactory recovery, but on at least two occasions she had marked impairment of conjugate gaze and at times seemed somewhat confused and flightly in her ideas.

DISCUSSION

It is readily apparent from the preceding case histories that there is no characteristic history in craniopharyngiomas occurring in older people, and the diagnosis may not be evident, especially when roentgenograms of the skull are negative, until air studies are done.

Headaches: Headaches occurred late in the clinical course in three cases and early in three. (In younger subjects, headache is almost invariably an early symptom.) The character or location of the headache was of no help in differential diagnosis.

Signs of increased intracranial pressure, such as nausea, vomiting, and papilledema, rarely occur in older persons.

This was true in this study, with the exception of case 5.

Visual disturbances occurred sooner or later in every one of the cases, early in the course from direct pressure on the optic nerve, chiasm, or tract, and later from increased intracranial pressure.

Visual field defects are not of differential value in this type of tumor, since there is great variation in the type and extent of the visual defects encountered. In adults the most frequent defect is a bitemporal hemianopsia. In this series, a left homonymous hemianopsia was found in two cases, a bitemporal hemianopsia in one, and normal visual fields in only one case. In two of the cases, fields could not be done because of lack of cooperation.

Fundi: While papilledema is very common early in the course of the disease in children, temporal pallor of the disks or definite optic atrophy is more usual in adults. Frequently the papillae are normal in adults. A peculiarity of the funduscopic picture noted particularly in suprasellar cysts occurring in older persons is pallor of the temporal halves of the disks suggestive of optic atrophy, and edema of the nasal halves suggestive of papilledema. In this series, there was pallor of the disks in three cases, normal papillae at first, with late development of papilledema in two, and normal fundi late in the course of the disease in only one (case 5).

Extraocular palsies: There was late development of a partial bilateral third nerve palsy with external strabismus in case 6, and a left internal strabismus in case 4.

Pupillary abnormalities: In four of the cases the pupils reacted sluggishly to light. In case 2 there was an anisocoria.

Diplopia: There was no complaint of diplopia in any of the cases. Beckman and Kubie[5] have described diplopia occurring as a result of heteronymous defects in the visual fields, with relative reduction of macular vision, preventing the use of heteronymous fields for binocular vision, with resulting diplopia.

Hypothalamic symptoms: Of great clinical significance and an aid to localization were the symptoms produced by involvement of the hypothalamus, that is, polydipsia, polyuria, polyphagia, hyperthermia, somnolence, and pulse and temperature dissociation. The episodes of hyperthermia were prominent in the history in case 5. In this group somnolence was a rather frequent symptom, occurring in four of the cases. This is not in accord with the observations of Kubie and Beckman, who described somnolence as occurring late in the clinical history, and practically confined to children and young adults.

Endocrine disturbances of a regressive sexual nature, such as loss of libido, obesity, and hair dystrophy, were noted in these histories. Loss of libido occurred in three cases. An early menopause ensued in one of the cases. At least two of the women were married, and one was the mother of two children. No woman was married in Beckman and Kubie's series. Among the men, a late marriage was noted in two cases, and infertility in one. Hair dystrophy occurred in case 3. Obesity was present in four of the six cases, with loss of weight noted in cases 1 and 3.

Urinary incontinence occurred in three cases.

Symptoms and signs due to pressure upon the brainstem, basal ganglia, thalamus, and efferent cerebellar pathways. Evidence of pressure on the brainstem manifested by attacks of decerebrate

rigidity was found in cases 1 and 2. Unilateral, or more often bilateral pyramidal tract signs, and motor weakness were found, due to pressure on the cerebral peduncles. Van Bogaert described thalamic and parkinsonian syndromes in craniopharyngiomas following the stage of their intraventricular growth. Case 3 walked with small steps; case 4 tended to festinate in walking early in the history. In case 1 the brief episodes of dysesthesias accompanied by a sense of panic could well be attributed to involvement of the thalamus. Bailey[2] has described the cerebellar symptoms produced by suprasellar tumors, and he stated that the most likely mechanism by which the functions of the cerebellum are disturbed is compression of the superior cerebellar peduncles against the edge of the tentorium. Perhaps cerebrocerebellar connections may also be interrupted. Cerebellar symptoms were observed rather often in these cases. An ataxic gait was present in case 6, case 3, and late in the course in case 1. An intention tremor of both upper extremities occurred in case 6. Nystagmus on left lateral gaze was noted in case 1.

Anosmia was present in cases 1 and 3.

LABORATORY FINDINGS

Cerebrospinal fluid exhibited no consistent abnormalities. An elevated protein was found in three cases, and a pleocytosis in two.

Suprasellar calcifications were found in three cases.

Electroencephalogram: Of particular interest were the electroencephalographic findings in case 2. The first record, taken when the patient showed many neurologic signs, was very abnormal, with a huge left-sided focus, and mirror focus on the right. For some unexplained reason, perhaps a temporary decrease in edema about the tumor, he suddenly became asymptomatic and had a normal neurologic status for a while. This was coincident with a marked improvement in the electroencephalogram, although focal signs on the left still remained. In case 3 the electroencephalogram was normal.

PROGNOSIS

Out of the six cases, four died. The two that survived made fairly good immediate recoveries, but have not been followed up.

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Treatment of Intracerebral Hematomas in Young and Middle-aged Patients

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INTRACEREBRAL HEMATOMAS have been diagnosed with reasonable accuracy, particularly in older patients, for many years. Recent trends in neurosurgical practice indicate that a more aggressive attitude toward the perplexing problems associated with such lesions may, through early judicious surgical intervention, unexpectedly salvage many patients.

Intracerebral hematomas are described most commonly as hemorrhagic mass lesions (blood clots) located within the substance of the cerebral hemispheres or adjacent cerebral ganglia. Those hematomas occurring in the cerebellum or brainstem usually are specifically so designated. By dissection through pressure, an intracerebral blood clot may extend to communicate with the cerebral subarachnoid spaces or the ventricular pathways; however, it may be completely contained within the substance of the brain, as is a tumor.

Many underlying diseases are recorded as associated with cerebral hemorrhage, such as arteriosclerosis, hypertension, cerebral aneurysms, cardiovascular anomalies, brain tumors and abscesses, intracranial vascular occlusion, periarteritis nodosa, lupus erythematosus, tuberculosis, syphilis, eclampsia, trauma, blood dyscrasias, and scurvy. Treatment with heparin or other anticoagulants also has been blamed.

The average age of patients who have intracerebral hemorrhage was noted by Brown[1] to be 53 years. In general, most reports of surgical intervention in this disorder have been concerned with patients in the older age groups. Understandably, the results of neurosurgical intervention in older people who suffer from intracerebral hemorrhage are at times discouraging and have led to some pessimism as to the efficacy of operative intervention in patients who have intracerebral bleeding.

A survey of the literature,[2–13] however, reveals that relatively little attention has been paid to the surgical treatment of this disorder in younger patients. We recently have observed and treated surgically at the Mayo Clinic seven patients between 19 and 53 years of age who had intracerebral hematomas. It appeared

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desirable to report our experience with these patients, as well as to indicate the results of surgical intervention.

REPORT OF CASES

Case 1.—A 38 year old white woman with known hypertension group 3 of several years' duration was admitted to the hospital in coma in September 1953. Relatives stated that in August 1953 the patient noticed a sudden onset of clumsiness of the right arm and leg that cleared spontaneously during a two-week period. However, in September a sudden headache was experienced, and the patient became drowsy, vomited, and had difficulty using her left arm and leg. Some improvement occurred, but four hours later coma ensued and the patient showed evidence of left hemiparesis.

At the time of the patient's admission, the blood pressure was 200/120. The pulse was 60 beats per minute. Ophthalmoscopic study revealed retinopathy indicative of hypertension group 3 (Keith-Wagener). Results of laboratory studies were essentially normal and roentgenograms of the skull were interpreted as normal. A tentative diagnosis of intracerebral hemorrhage secondary to hypertension was made. Because of the focal neurologic signs, the patient's youth, and the evidence of increased intracranial pressure, diagnostic ventriculography was done, which demonstrated a pronounced shift of the ventricular system to the left. Subsequent craniotomy disclosed an acute intracerebral hematoma in the posterior frontal region. The hematoma which was evacuated measured approximately 4 cm. in diameter.

The patient rapidly regained consciousness after the operation, and postoperative convalescence was uneventful. With physical therapy the hemiparesis began to improve and the hypertension was treated with continuous intravenous injection of alkavervir (Veriloid), followed by combined therapy with hydralazine hydrochloride (Apresoline) and hexamethonium. Two months after evacuation of the hematoma the patient was alert, well oriented, and walked with the aid of a cane; her blood pressure was 150/110. She was receiving anticonvulsant therapy because of the recurrence of several minor convulsive seizures involving the left side of the face.

At first glance this patient presented a history typical of a cerebrovascular accident due to hypertension. However, with the early improvement in her neurologic status after the initial insult, followed by a second episode with coma and signs of increasing intracranial pressure, intracerebral hematoma appeared likely. One may speculate that an initial leak from an intracranial vessel passing through the cerebral pathways for subarachnoid fluid may, with healing, seal off these spaces and increase the tendency for subsequent bleeding to rupture into the substance of the brain.

The slow return of function of the paralyzed side in this patient coincides with the findings of Courville and Blomquist,[14] who wrote that hemorrhage due to nontraumatic conditions occurred most often in the region of the internal capsule, while hemorrhage due to trauma was found more commonly in the more superficial portions of the cerebral hemispheres. This is illustrated in the next case.

Case 2.—In October 1953 a 19 year old white boy was admitted to the hospital in a semicomatose state after an injury to the head. Witnesses stated that the patient fell during a fist fight, striking his head and losing consciousness. On regaining consciousness, he experienced a severe headache and vomited; 12 hours later he became confused. The mental confusion slowly increased until the patient was irrational and semicomatose.

On examination he was drowsy and uncooperative. Multiple bruises of the face were noted, with swelling and ecchymosis of the left eye. The blood pressure was 130/80 and the pulse rate was 40. The plantar and deep reflexes were normal. Funduscopic examination revealed early choking. Results of laboratory studies were normal, and roentgenograms of the skull revealed a linear fracture of the right temporal bone.

Because of fluctuation of the degree of consciousness and the presence of bradycardia and mild papilledema, bilateral temporal trephination was done to exclude the possibility of

extradural or subdural bleeding. The cortex of the left hemisphere appeared deeply discolored, and immediate ventriculography demonstrated a shift of the lateral ventricles to the right. At subsequent craniotomy a large acute intracerebral hematoma in the left temporal lobe was removed without incident. The postoperative course was uneventful; examination revealed that the degree of papilledema had receded. Visual fields were normal, and the patient was later able to resume his university studies.

Case 3.—A 53 year old white man was admitted to the hospital in November 1953 in a semicomatose state. His relatives stated that the patient had been unable to speak and had had weakness of his right side for at least two days previously. The patient was known to consume large quantities of alcoholic beverages. Twenty-four hours before admission he had fallen from a porch. The initial thought of his family was that his semicomatose state was due to alcoholism.

Blood pressure was 130/74. The pulse rate was 90. He was semistuporous and exhibited right hemiparesis and partial aphasia.

The ocular fundi were normal. Results of laboratory studies and roentgenography of the skull were normal. On the second hospital day the patient was less alert and hiccuped; an increase in the aphasia and hemiparesis was noted.

Because the patient showed progressive cerebral dysfunction, bitemporal trephination of the skull was done. No subdural or extradural blood was found, but the left temporal region appeared discolored and contused. Ventriculography revealed a shift of the ventricular system to the right, and subsequent craniotomy demonstrated a large acute intracerebral hematoma in the posterior temporal region. Fresh and old clots were evacuated. One month after operation the patient was able to read slowly and speak well; the right arm and leg were normal in strength. He returned to work three months after operation, making continued progress toward recovery.

These last two patients were admitted to the hospital because of known trauma to the head. Each patient showed signs of increasing intracranial pressure, and a tentative diagnosis of subdural hemorrhage was made in each prior to operation. After negative results of bitemporal trephine exploration for subdural hemorrhage, the difficulty of explaining the neurologic deficits as a result of contusion, cerebral edema, or an intracerebral mass lesion presented a surgical problem solved by diagnostic ventriculography. In each case there was evidence of a shift of the ventricular system due to intracerebral hemorrhage in the temporal lobes.

Pilcher[15] reported that four of eight patients treated surgically for intracerebral hemorrhage had discoloration of the cerebral cortex over the hematoma. This was present in these two cases in our series.

Case 4.—A 39 year old white man was admitted in October 1953 because of coma and right hemiplegia of a day's duration. Two months before, the patient had complained of frontal headaches and blurring of vision. He had been admitted to the local hospital because of fever and generalized rash; a diagnosis of endocarditis was made and antibiotics were given for six weeks.

One month prior to admission to the clinic, he had had thrombophlebitis; because of certain signs and symptoms, including headache and coughing, the diagnosis of cerebral and pulmonary emboli was made. A month later, one day prior to our initial examination, sudden severe headache, numbness, and weakness of the right side of his body developed. Because blood was found in the cerebrospinal fluid, a cerebrovascular accident appeared likely and the patient was sent to the clinic.

The patient was semicomatose. The blood pressure was 142/80. His neck was stiff and he was unable to move the right arm and leg. Ophthalmoscopic examination showed no abnormalities. The erythrocytic sedimentation rate was 56 mm. during the first hour (Westergren method). Roentgenograms of the skull revealed equivocal shift of the pineal body to the right. Electroencephalographic tracings showed a delta-wave focus grade 3 (3 to 5 cycles per second) in the left temporo-occipital area. Cerebrospinal fluid obtained at lumbar

puncture was crystal clear, colorless, and under a pressure of 400 mm. of water. The initial culture of blood revealed *Micrococcus albus* but subsequent cultures showed no growth. Two weeks after admission to the hospital ophthalmoscopic examination of the ocular fundi showed full retinal vessels and early papilledema. An angiogram of the left internal carotid artery demonstrated shifting of the left anterior cerebral arterial complex to the right, and confirmatory ventriculography revealed the ventricular system to be displaced to the right by a mass lesion in the left temporoparietal region. A large intracerebral hematoma extending from the left posterior frontal region to the occipital region was subsequently removed without incident.

After operation the patient evidenced slow but progressive improvement of the paralysis of the right arm and leg. Evidence of aphasia was absent. Two months after operation he had made considerable progress toward recovery but had not yet returned to work.

Case 5.—A 35 year old white man was first admitted to the clinic in August 1953, because of headache and progressive weakness on the left side for three weeks. The blood pressure was 110/65, and the pulse rate was 60. The ocular fundi were normal. Neurologic examination disclosed left hemiparesis. Roentgenograms of the skull revealed no abnormalities except calcification of the falx cerebri. Electroencephalographic tracings were within normal limits. Because of progressive improvement, the patient was allowed to leave the hospital but was cautioned to remain in town.

A few days later he experienced onset of numerous and persistent seizures involving the left arm and shoulder. Headache was not prominent, but because of the numerous unilateral seizures the patient was rehospitalized. Results of examination on this admission were essentially unchanged from those noted previously.

An angiogram of the right internal carotid artery was interpreted as normal. Diagnostic pneumoencephalography, however, demonstrated the ventricular system to be displaced to the left. At craniotomy a cystic intracerebral hematoma in the superior and posterior frontal region of the right cerebral hemisphere was encountered and evacuated. The patient's postoperative convalescence was uneventful; he was gradually regaining use of his left arm and leg when he was last seen three months after operation.

Case 6.—A 26 year old white man was admitted to the clinic in November 1953, because of left hemiparesis of one day's duration. The patient had awakened the night before admission with a headache, at which time he discovered weakness of the left arm and leg. According to relatives, the patient's speech became progressively slurred and he gradually became stuporous.

Blood pressure was 140/78, and the pulse rate was 52. The patient was excessively drowsy. Pronounced nuchal rigidity and left hemiparesis were present. Results of laboratory studies and roentgenograms of the skull were normal. Ophthalmoscopic examination showed the ocular fundi to be normal. Electroencephalography revealed a delta-wave focus grade 2 in the right temporoparietal region. Cerebrospinal fluid obtained at lumbar puncture was found to be bloody and under increased pressure. A tentative diagnosis of ruptured intracranial aneurysm was made.

On two separate occasions bilateral carotid angiograms did not demonstrate a lesion. Because the patient failed to show adequate improvement as the result of conservative therapy, a diagnostic pneumoencephalogram was undertaken which revealed a large air-filled cavity communicating with the right lateral ventricle and suggestive of a mass encroaching on the lateral ventricle. At subsequent craniotomy a large cystic intracerebral hematoma in the right parietal motor area was uncovered and found to communicate with the right lateral ventricle.

The patient's postoperative course was complicated by severe cerebral edema, necessitating reelevation of the bone flap. Subsequent convalescence was uneventful and the weakness of the left leg gradually improved; however, the left hand still remained weak when the patient was dismissed from the hospital 28 days after operation.

Case 7.—In July 1953 a 53 year old white man was admitted to the clinic because of confusion, aphasia, and right hemiparesis of four weeks' duration. The patient's relatives stated that six months prior to admission he had complained of headaches and blurred vision. One month prior to admission he had become con-

fused, noted difficulty using the right leg and arm, and had undergone a change in personality. A tentative diagnosis of a brain tumor was made by the local physician and the patient was sent to the clinic.

The patient was confused and semistuporous. Blood pressure was 140/90. Sensory and motor aphasia appeared to be present, and the patient's right side was paretic. The ocular fundi were normal, and electroencephalograms showed a focus producing waves of 5 to 7 cycles per second in the left temporal region. Results of laboratory studies were normal. Roentgenograms of the skull gave evidence of displacement of the pineal body to the right.

Because it was obvious that the patient was suffering from increased intracranial pressure, presumably due to a mass lesion in the left hemisphere, left craniotomy was done, disclosing a large intracerebral hematoma in the lower left parietal lobe. During the patient's postoperative convalescence, the aphasia and right hemiplegia showed progressive improvement. He was able to be dismissed on the nineteenth postoperative day.

The presenting complaint of each of the last four patients was progressive hemiparesis ranging from one day to four weeks in duration, headache for several weeks prior to the onset of the hemiparesis, and stupor. These symptoms are also commonly associated with intracranial neoplasms. It is worthy of note that results of cerebral angiography in two of these four patients were interpreted as within normal limits, but diagnostic pneumoencephalography or ventriculography revealed evidence of an intracranial mass.

COMMENT

At the present time, it is obviously unreasonable to subject a large number of severely hypertensive arteriosclerotic elderly patients with intracerebral hemorrhage to major intracranial surgical procedures with expectation of gratifying results in the majority of instances. However, cerebral hemorrhage is not necessarily the prerogative of the elderly hypertensive arteriosclerotic patient. It may occur in patients of any age group, as emphasized by Effron and associates,[16] who reported two such cases in children.

We believe that the results in these seven patients, whose ages ranged from 19 to 53 years, demonstrate that surgical removal of cerebral hematomas in young and middle-aged patients is effective. The reasons for successful treatment in patients of this age group are many. However, the absence of severe arteriosclerosis as well as of hypertension (in all but one of our patients) is of major importance. Trauma is more likely to play a role in patients of this age range than it is in the usual instances of intracerebral hematoma. Other causes of hemorrhage, such as septicemia and endocarditis, may be found. However, as was noted in three of our patients, it is impossible at times to determine the exact reason for the intracerebral bleeding.

While the correct diagnosis of intracerebral hemorrhage can be made without too much difficulty in older patients, such is not the case in younger patients. As shown in this study, it is extremely difficult to make a preoperative diagnosis between hemorrhage and other causes of expanding intracranial lesions. Consequently, the diagnosis of intracerebral hemorrhage in younger persons frequently is made only at the time of operation. It would appear axiomatic, therefore, that ventriculography and arteriography should be employed in young and middle-aged patients who possibly might have intracerebral hemorrhage. This is particularly true of any patient suspected of having a subdural hematoma and in whom no such subdural hematoma is found at operation.

SUMMARY

A study has been made with regard to intracerebral hematomas in young and middle-aged patients as diagnosed and treated in seven patients at the Mayo Clinic. These hematomas were due to various causes and the patients presented a variety of clinical data, so that it was extremely difficult to make an accurate diagnosis of intracerebral hemorrhage prior to surgical intervention. All patients recovered to some degree after operation. Two have been able to return to their previous employment. It is suggested that the surgical removal of intracerebral hematomas in young and middle-aged patients is effective and is the treatment of choice in most instances.

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Cerebrospinal Fluid Gamma Globulin as a Diagnostic Test for Multiple Sclerosis

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MULTIPLE SCLEROSIS is a diagnosis made almost solely on the basis of the history of the illness and the clinical findings. The only laboratory examinations that have shown a consistent tendency to abnormality have been those measuring the globulin fraction of the protein in the cerebrospinal fluid. The colloidal gold reaction of the spinal fluid is frequently abnormal,[1] and further refinements of the test increased the correlation of a certain type of abnormal curve (D type) with the diagnosis of multiple sclerosis.[2] Direct measurement of the gamma globulin in the cerebrospinal fluid by immunochemical methods revealed elevation of this fraction of the protein in a high percentage of patients with multiple sclerosis.[3,4] Electrophoretic measurement of spinal fluid has confirmed the finding of abnormal protein patterns with elevation of the globulin fractions, particularly gamma globulin.[5,6]

Within recent years, two new chemical photometric methods for determining spinal fluid gamma globulin have been developed.[7,8] One of these is a fairly simple procedure involving precipitation of the protein with zinc sulfate in barbital buffer at a pH of 7.3, as described by Kunkel[9] and used on cerebrospinal fluid by Donovan and associates.[10] Using this test, Roboz and co-workers[8] obtained significantly higher values for gamma globulin in cerebrospinal fluid specimens from patients with multiple sclerosis than from those with other neurologic diseases. The specificity of this method was checked against the electrophoretic method and was thus shown to be satisfactory.

In the present study this zinc sulfate method for determining gamma globulin was carried out on the spinal fluids of a heterogenous group of patients in order to determine the diagnostic value of the test and the incidence and nature of false negatives and positives. Particular attention was paid to the relation of the total protein of the spinal fluid to the amount of gamma globulin, as well as the relation of the latter to the colloidal gold reaction of the spinal fluid.

MATERIAL

Specimens of spinal fluid from a series of 200 patients were examined. Clinical charts on all patients were carefully studied and on this basis, four groups were constructed:

1. Nineteen patients with clinically diagnosed late multiple sclerosis. These

From the division of neuropsychiatry and the laboratories of the medical division, Montefiore Hospital, New York City.
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patients almost all had prolonged study, typical histories, and signs of multiple lesions.

2. Eleven patients with early disease, questionable or atypical histories, and findings of multiple sclerosis.

3. One hundred and thirty-four patients with diverse neurologic disease clinically not multiple sclerosis. This group included the usual kinds of conditions seen in both in- and outpatient neurology departments, for example, cerebral thrombosis, amyotrophic lateral sclerosis, migraine, and so on.

4. Thirty-six patients with no neurologic disease. These spinal fluids were for the most part from an unselected group of patients who had spinal anesthesia for surgery on pelvic or abdominal organs. Five specimens were from patients with hepatic cirrhosis or multiple myeloma, selected because of the relation of spinal fluid protein to altered serum proteins.

PROCEDURE

Total protein of cerebrospinal fluid was determined by the method of Denis and Ayer,[11] in which the protein is precipitated with sulfosalicylic acid and the resulting turbidity is compared with that of a standard protein solution similarly treated. During the course of the investigation the method was checked by determining the total protein in a large volume of spinal fluid by the usual micro-Kjeldahl procedure.

Gamma globulin was determined by the method described by Roboz and coworkers,[8] in which the gamma globulin is selectively precipitated by zinc sulfate at a pH of 7.3. The precipitate thus separated is then washed and determined photometrically with the phenol reagent of Folin and Ciocalteau.[12] It was found that the colored solution had an absorption maximum at 660 millimicrons; therefore all measurements were made at this wave length in contrast to the value of 460 given by Roboz.

Values obtained by the electrophotometer were checked against standard solutions which had been made from a sample of gamma globulin supplied by the Commission on Plasma Fractionation of the Harvard School of Public Health. This material had shown an estimated 100 per cent assay of gamma globulin by electrophoretic measurement. Two determinations were made on each sample of spinal fluid. Absolute values for gamma globulin, and its percentage of the total protein were calculated.

It was apparent that in our cases the absolute values for gamma globulin, although elevated in many cases with multiple sclerosis, were not as diagnostic as was an elevation of its percentage of the total protein. We therefore relied solely on this latter value to evaluate the procedure, and, following Kabat and coworkers[2] as well as Roboz, who obtained approximately similar results, we selected 13 per cent of total protein as the upper limit of normal. Forty-five mg. per cent was considered the upper limit of normal for total protein in spinal fluid.

RESULTS

Spinal fluid findings for total protein and gamma globulin percentage of total protein for the four groups of patients are presented in tables 1 to 4.

False positives: The value of the test depended to a large degree on the number, and particularly the nature, of the false positives obtained. The clinical diagnoses, therefore, of those patients who did not have multiple sclerosis but showed elevated spinal fluid gamma

TABLE 1

PATIENTS WITH LATE MULTIPLE SCLEROSIS

Gamma globulin greater than 13%	14
Total protein normal	10
Total protein elevated	4
Gamma globulin less than 13%	5
Total protein normal	2
Total protein elevated	3
Total	19

Note: Highest total protein value in this group was 61 mg. per cent.

TABLE 2

PATIENTS WITH QUESTIONABLE MULTIPLE SCLEROSIS

Gamma globulin greater than 13%	8
Total protein normal	7
Total protein elevated	1
Gamma globulin less than 13%	3
Total protein normal	2
Total protein elevated	1
Total	11

TABLE 3

PATIENTS WITH NEUROLOGICAL DISEASE OTHER THAN MULTIPLE SCLEROSIS

Gamma globulin greater than 13%	29
Total protein normal	12
Total protein elevated	17
Gamma globulin less than 13%	105
Total protein normal	69
Total protein elevated	36
Total	134

TABLE 4

PATIENTS WITHOUT CLINICAL NEUROLOGICAL DISEASE

Gamma globulin greater than 13%	11
Total protein normal	10
Total protein elevated	1
Gamma globulin less than 13%	25
Total protein normal	16
Total protein elevated	9
Total	36

TABLE 5

Diagnosis	*No. of Cases*	*Per cent gamma globulin Total protein (mean)*	*Total protein mg. per cent (mean)*
Cerebral thrombosis	5	14.5	67
CNS lues	5	16.8	40
Post-tuberculous meningitis syndrome	3	20.5	63
Brain tumor	2	18	105
? Acute demyelinating encephalitis	2	34	29
Peripheral neuritis	2	15	129
? Schilder's disease	1	13	31
? Late stage of virus or demyelinating encephalitis	1	26	19
Choreiform movements in patient with lymphoma treated with nitrogen mustard	1	21	61
Abrupt onset 3rd nerve palsy unknown etiology	1	21	27
Progressive cerebellar disease	1	19	31
Uremia, coma, CSF pleocytosis	1	17	39
Diabetes, seizures	1	15	53
	26		

Note: In 3 cases spinal fluids with demonstrable blood were examined (spontaneous hemorrhage 2 cases, traumatic 1 case). Mean gamma globulin percentage was 14.5, mean total protein was 61 mg. per cent.

globulin values are given in table 5, along with the mean gamma globulin and total protein values.

Table 6 gives data similar to table 5, except for those patients without symptomatic neurologic disease. Five of these patients (those with hepatic cirrhosis, multiple myeloma, and Boeck's sarcoid) had hyperglobulinemia and reversal of the albumin/globulin ratio.

Two of the four cases under "other" may have had syphilis. One patient ad-

TABLE 6

	No. Cases	Per cent gamma globulin	Total protein
Latent neurosyphilis (CSF)	2	17, 19	20, 17
Multiple myeloma	2	36, 40	36, 18
Hepatic cirrhosis	2	27, 26	39, 29
Boeck's sarcoid	1	26	17, 8
Other	4	18, 16, 17, 17	52, 22, 47, 22

mitted for study of headaches and an upper respiratory infection had a history of treated syphilis and showed bilateral Babinski signs on examination. A second youthful patient had an aneurysm of the arch of the aorta, although no other evidence for syphilis was found. Of the two others, one had polycystic kidneys with superimposed hypernephroma (blood proteins and serologic reaction were normal), and the last patient following a prostatectomy had hallucinations, became comatose, and died of an undiagnosed condition.

Colloidal gold: Colloidal gold reactions were done by the Albany State Laboratory using the Lange modification on only 48 out of the total of 200 spinal fluids on which gamma globulin determinations were carried out. In patients with multiple sclerosis, it was found that a high gamma globulin usually corresponded with a high D type colloidal gold curve (six patients). A high B curve occurred, however, in the cerebrospinal fluid of one patient with multiple sclerosis associated with an elevated gamma globulin value and a low D curve in another. On the other hand, the cerebrospinal fluid of one patient with multiple sclerosis gave low gamma globulin value and a high D colloidal gold curve.

There were 26 other spinal fluids which showed abnormal colloidal gold reactions. In general, wherever gamma globulin values were high, colloidal gold curve abnormality appeared, but slight to moderate abnormality of colloidal gold reaction was seen in spinal fluids from a wide variety of patients, with or without elevated gamma globulin values.

Repeated determinations of gamma globulin: After a variable time interval, a second spinal fluid examination was performed on 13 patients, some with values that had been elevated in the first sample, others with normal values. The time interval was, in all except a few, two to four months. In ten cases the percentage of gamma globulin varied four per cent or less from the original value; in the following three cases there was a marked difference.

Case 1.—A young woman thought clinically to have had demyelinating encephalomyelitis showed 43 per cent spinal fluid gamma globulin within a few weeks after her acute illness. Weeks later, after clinical improvement, gamma globulin was 15 per cent of total protein. Total protein value on first examination was 26 mg. per cent, on second 32 mg. per cent.

Case 2.—A young woman with obscure myelopathy, probably multiple sclerosis clinically. Spinal fluid gamma globulin was 23 per cent of total protein on one occasion, 15 per cent a few months later. Total protein in spinal fluid was low, however (18 mg. per cent on one occasion, 23 per cent on another) and the absolute gamma globulin values therefore varied little (3.5 to 4.0 mg. per cent).

Case 3.—A child with clinically diagnosed Schilder's disease in advanced state of spasticity and dementia. Spinal fluid gamma globulin 6 per cent on one occasion, 13 per cent a few months later. Spinal fluid total protein was normal.

COMMENT

The finding of Roboz and co-workers[8] that the zinc sulfate precipitation method for determining spinal fluid gamma globulin yields a high percentage of abnormal values in patients with multiple

sclerosis is confirmed and as such it is a useful ancillary procedure to the diagnosis of this disease. Unlike Roboz, we did not find commonly a second type of spinal fluid pattern in multiple sclerosis —high spinal fluid protein with low ratio of gamma globulin.

Important to the clinical usefulness of a test is the incidence of false positives. It is apparent from the data presented here, as well as from that of Roboz, and of Kabat[13] using the immunochemical method, that many patients without multiple sclerosis show elevation of spinal fluid gamma globulin. Many such individuals suffer either from central nervous system syphilis (which in our small series gave moderate elevation of gamma globulin) or elevation of serum globulin due most commonly to multiple myeloma, hepatic cirrhosis, or Boeck's sarcoid (all cases of which give extreme elevations of gamma globulin). Most of these patients had normal total protein values in the spinal fluid.

Another patient group with abnormal gamma globulin had either markedly elevated spinal fluid proteins or cerebral thrombosis with possibility of some leakage of blood into the spinal fluid. The latter two conditions caused a rise in gamma globulin to values slightly above 13 per cent as did frank blood in the spinal fluid seen in three cases. Using this method, it may well be profitable, therefore, to consider as definitely pathologic only gamma globulin percentages exceeding 15 per cent of total protein.

Two very high values of gamma globulin were seen in patients diagnosed as postencephalomyelitic state. One of these patients had received a course of virus therapy (Egypt 101) for multiple cutaneous metastases of a carcinoma of uncertain origin and had rapidly developed signs and symptoms of encephalitis; the second had developed spontaneously a syndrome thought to be acute demyelinating encephalomyelitis.

There still remain, after removal of these cases, two or three cases with unexplained high values. Not all of these patients, however, had diagnostic studies which excluded abnormality of serum proteins.

Parenthetically, it appears that in central nervous system syphilis gamma globulin may be abnormal in the absence of positive serologic reactions in the spinal fluid. One 45 year old patient, for example, with a known history of syphilis adequately treated several years prior to admssion, suffered from mental deterioration and neurologic deficit involving pyramidal tract pathways and basal ganglia. Blood serologic reaction was positive, although spinal fluid was negative, gamma globulin being elevated.

Normal gamma globulin values or false negatives were seen in many patients clinically diagnosed as multiple sclerosis, as they have been in other series.[8,13]

In speculating on the reason for this fact, four possibilities may be considered:

1. Were the patients not suffering from multiple sclerosis? It is doubtful if this accounts for more than a few cases, since several late or classical cases and one autopsy-proved case have had normal gamma globulin values.

2. Were the gamma globulin values laboratory errors? Two determinations were run on each spinal fluid, thus minimizing chance of a laboratory error. Furthermore, normal gamma globulin values in a certain percentage of patients with multiple sclerosis has been a con-

sistent report by other investigators using various methods.[13]

3. Does the spinal fluid gamma globulin in some cases fluctuate, perhaps reaching higher values with each attack and dropping as the disease becomes chronic? That this course may occur is suggested by two of our cases: The first, a patient with abrupt onset of diffuse signs suggestive of demyelinating encephalomyelitis in whom the gamma globulin was 43 per cent of the total protein a few months after the onset of her illness and 25 per cent a few months later, after clinical improvement; the second, a case of chronic multiple sclerosis (proved by autopsy) in whose spinal fluid 8 per cent of protein was gamma globulin, whereas, several years earlier it had been found to be 22 per cent by the immunochemical method of Kabat. Whether this drop occurs in a sizable number of individuals is doubtful since most late cases show elevated values. Yahr and co-workers[13] considered this question in studying the incidence of gamma globulin elevation in their large series of patients with multiple sclerosis. They found no correlation between gamma globulin values and the duration of the disease, the nature of onset, or the time elapsed since appearance of new symptoms. The possibility exists, however, that a transient rise and fall of gamma globulin can follow clinical symptomatology in some individuals who recover completely from attacks of multiple sclerosis. Only repeated examinations on this group of patients during attacks and symptom-free intervals will shed light on this question.

4. Does the normal gamma globulin differentiate a special group of patients in whom failure of gamma globulin responses in cerebrospinal fluid is only a facet of a disease process different from the ordinary multiple sclerosis?

Relevant information to this most interesting possibility is the fact that the spinal fluid gamma globulin is, in multiple sclerosis, almost undoubtedly derived from the central nervous system, since alterations in blood proteins are minimal.[5]

SUMMARY AND CONCLUSIONS

1. Spinal fluids from 200 patients were examined for gamma globulin by the zinc sulfate precipitation method.

2. Considering any gamma globulin value that exceeded 13 per cent of the spinal fluid total protein as elevated, it was found that 73 per cent of patients with multiple sclerosis and 26 per cent of patients without multiple sclerosis gave elevated values.

3. Outside the multiple sclerosis group, a large number of high gamma globulin percentage values occurred in patients with central nervous system syphilis and in patients with marked elevation of serum globulin.

4. Nine cases with high cerebrospinal fluid total proteins or with a diagnosis of cerebral thrombosis gave mean gamma globulin percentages of 14.5 to 15 per cent, as did three cases with frank blood in the cerebrospinal fluid. Using this method, it was be well to consider only percentages of over 15 per cent as definitely abnormal at any level of spinal fluid protein.

5. Repeated examinations of spinal fluid after a time interval showed closely similar values except for three cases, in one of which a marked fall in gamma globulin correlated with clinical improvement from an acute disease thought to be demyelinating in nature.

6. In a small series, elevated spinal fluid gamma globulin was most often

correlated with a high Lange D colloidal gold curve.

7. Possible reasons for the normal cerebrospinal fluid gamma globulin seen in some cases of multiple sclerosis are commented upon.

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■ Mr. Longet thinks that the gray matter of the spinal cord cannot be a conductor of sensitive impressions, because it is not endowed with sensibility; and his single argument to prove that the posterior columns are the sole conductors of the sensitive impressions is, that they are the only sensitive parts of the spinal cord. On another side, he admits that the cerebellum, which he rightly believes not to be sensitive, is the principal channel for the transmission of the sensitive impressions. Of course, if the gray matter of the spinal cord cannot be a conductor, because it is not sensitive, the cerebellum also cannot be a conductor; and if it is, the gray matter also can be.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

A New Scale for Evaluating Disability in Multiple Sclerosis

John F. Kurtzke, M.D.

IT HAS LONG BEEN APPARENT that an objective and reproducible method of evaluating patients with multiple sclerosis was necessary. Next to the unpredictable course for the individual with this disease, the absence of such a means of measuring disability has been a prime factor in the known difficulty of evaluating proposed therapies in multiple sclerosis. Prior attempts at mensuration range from the all-or-none categorization of MacLean and Berkson[1] (incapacitated or not incapacitated) to the complex schema of Alexander,[2] but there is no generally accepted scale in present use.

The goal of a rating-scale is threefold: 1) that the sum-total of any patient's disabilities should fit him into a suitable category; 2) that any change in disability should be reflected in a corresponding change of status; and 3) that the scale be simple enough to be manageable.

The scale to be presented was devised to evaluate a possible therapeutic agent for multiple sclerosis.[3] In the course of that work over 300 cases of multiple sclerosis were studied; all were assignable in this scale. It was used to measure status on admission to and discharge from the hospital in order to establish a baseline with which to compare the in-hospital course of groups of patients.

STATUS IN MULTIPLE SCLEROSIS

0—Normal neurologic examination.
1—No dysfunction, minimal signs (Babinski, minimal finger to nose ataxia, diminished vibration sense).
2—Minimal dysfunction (slight weakness or stiffness, mild disturbance of gait, awkwardness, mild visuomotor disturbance).
3—Moderate dysfunction (monoparesis, mild hemiparesis, moderate ataxia, disturbing sensory loss, prominent urinary or eye symptoms, or combinations of lesser dysfunctions).
4—Relatively severe dysfunction not preventing ability to work or carry on normal activities of living, excluding sexual function. This includes the ability to be up and about 12 hours a day.
5—Dysfunction severe enough to preclude working, with maximal motor function walking unaided up to several blocks.
6—Assistance required for walking (canes, crutches, braces).
7—Restricted to wheelchair (able to wheel self and enter and leave chair alone).
8—Restricted to bed but with effective use of arms.
9—Totally helpless bed patient.
10—Death due to multiple sclerosis.

This scale is intended to measure the maximal function of each patient as limited by his neurologic deficits. Status 10 refers to death due to multiple scle-

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rosis[4] or its primary complication of bronchopneumonia. It excludes inanition, uremia, other infections, or coincident causes of exodus. Status 9 is self-explanatory. In status 8 falls the bed patient who has some use of his limbs — almost invariably the uppers; he can usually feed himself and perform part of his toilet. A patient of status 7 must be able to enter and leave his wheelchair by himself, but with the aid of trapezes or other devices as necessary, and further he must be able to wheel himself about. It does not include the patient who is tied in the chair and perambulated.

To rank in status 6, a patient must walk, for short distances at least, with the aid of crutches and/or braces. However, this would not include the paraplegic who walks by means of double long-leg braces and two crutches; such a patient would be status 7. Status 5 includes those who are too disabled to be up and about for long periods of time but who can ambulate without aid for fair distances; to totter unaided for a few steps does not so qualify one. To be placed in status 4, the patient's disabilities must be such that he can work or do housework, but this includes the ability to use public transportation, and primarily the ability to be ambulatory for most of the day. A patient so fatigued, weak, or ataxic that he must rest every half hour or so is not properly of this category. Categories 3 and 2 comprise those patients with mild dysfunctions. A combination of minor dysfunctions, or one relatively severe symptom (for example, monoparesis) describes status 3. In status 2 is the patient whose signs and symptoms, although in no way affecting usual functioning, are yet demonstrable; they are usually monosystemic and often are revealed by such complaints as stiffness, awkwardness, or fatigability. Category 1 is composed of asymptomatic patients in whom the neurologic examination is not normal. Category 0 comprises the normal, but includes 1) those with temporal pallor and normal visual acuity, 2) those with paresthesias but no sensory defect on examination, and 3) those with symptoms unsubstantiated by signs.

There are some patients whose allocation is not immediately apparent. If a paraplegic works, he is still a wheelchair patient, and assigned to category 7, not 4. On the other hand, the patient who will not utilize his capabilities is also met; this is he who lies abed contemplating his Babinski. In such a case one must estimate actual ability.

The patient whose symptoms are due solely to disturbance of head segment functions is also seen, although rarely. Among 315 patients with multiple sclerosis at this hospital, only seven such cases were found (2 per cent). Of course, this excludes those with a primary diagnosis of retrobulbar neuritis, for there must be the history or presence of other lesions in such patients in order to be given the diagnosis of multiple sclerosis. Of these seven patients, five had retrobulbar neuritis plus signs referable to other lesions, and two had normal visual functions. But even the patient with only optic manifestations can be classified. A small scotoma (not central) would call for status 1; minimal blurring, status 2; noticeably decreased visual acuity or large field defects, status 3; and more severe deficits status 4 or 5, depending on the degree of interference with functioning. Similarly other defects in head functions may be classified, but, as noted above, are rare without other dysfunction.

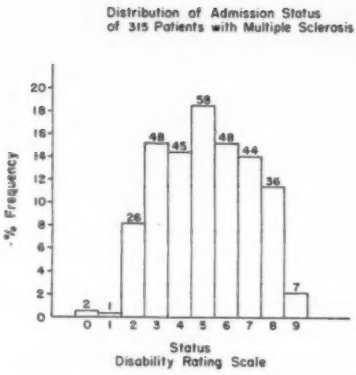

FIG. 1. Distribution of admission status of 315 patients with multiple sclerosis in accordance with the scale presented in this paper.

For the rest, the scale will be found appropriate to disability, since it is almost invariable that long-tract disturbances will be manifest most severely in the lower extremities, although a rare patient may be conversely affected. It will be noted that sexual functioning has been omitted from consideration, due to the impossibility of objective confirmation and to the influence of the emotional state on such behavior.

To illustrate the use of the scale, there is appended (figure 1) a graph showing the distribution of admission status of 315 cases of multiple sclerosis as grouped in this classification. It is apparent that, except at the extremes where such small numbers are to be expected, patients are well represented in each status, suggesting that none of these divisions are superfluous. The smooth bell curve indicates also that there are enough steps, and that the stages are roughly equal. To show that there is a sufficiency of steps to denote change, figure 2 is also presented; this represents the course in the hospital of 175 patients whose exacerbation leading to admission had persisted for two years or less. Of this group, one-third improved, one-sixth became worse, and the remainder were unchanged. This degree of change provides a basis against which therapeutic agents may be judged, when given to groups of patients on a short-term basis.

It is not claimed, nor is it necessary, that this scale provide an arithmetical progression of disability, that is, that status 4 is twice as bad as status 2; but it is a progression whereby disabilities may be matched, to denote the course of a single patient, or to compare groups of patients. The use of this scale need not be restricted to multiple sclerosis,

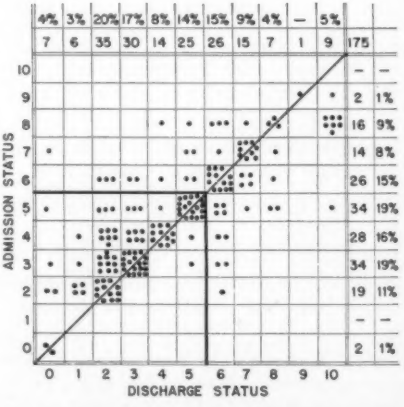

FIG. 2. Course in hospital of 175 patients with multiple sclerosis, whose exacerbation leading to admission has persisted for two years or less. The ordinate represents the status on admission in accordance with the scale presented in this paper; the abscissa similarly represents discharge status. The larger the status number, the more severe the impairment. Improvement is shown by a position to the left of the diagonal line; worsening, to the right. The boxes bisected by the diagonal line represent no change in status between admission and discharge. Each patient is represented by a dot. The position of each dot depends on admission and discharge status. For example, along 8 on the ordinate and 4 on the abscissa, is one dot, showing one patient admitted as status 8 and discharged as status 4, a gain of four categories. (Reprinted with permission from Am. Rev. Tuberc. 70:580, 1954.)

for many neuromuscular disorders lend themselves to such quantitation.

SUMMARY

A new classification of disability in multiple sclerosis is presented wherein a status number is provided in accordance with the patient's impairment due to neurologic dysfunction. The scale consists of ten progressive steps or classes. The scale has been applicable in the more than 300 patients studied at this hospital, and has proved satisfactory in measuring change in status of these patients during hospitalization.

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■ I have found that even the most sensitive nerve in the body, the trigeminal, loses its sensibility, its impressibility, in a part of its length. It is well known that a very considerable root of the trigeminal nerve goes down in the medulla oblongata towards the nib of the calamus scriptorius, being there between the anterior pyramid and the restiform body. Magendie has shown that a transversal section of one-half of the medulla oblongata dividing this root causes the loss of sensibility of the face, so that this root is positively a channel for the transmission of the sensitive impressions to the sensorium. Now, I have found that if a pin be introduced slowly and perpendicularly through the restiform body and the root of the trigeminal nerve in the medulla oblongata, there is no sign of pain, so that the impressibility of this root in that part of its length is lost, or at least notably diminished. This fact proves that the power of conducting sensitive impressions may exist in parts deprived of sensibility. Even when we compare the various parts of the length of roots and of the trunk of the spinal nerves, from the skin to the spinal cord, we find great differences in the degree of sensibility, while the conducting power seems to be the same everywhere.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Monthly Periodicity of Symptoms from the Central Nervous System

Erik Ask-Upmark, M.D.

IN A PREVIOUS PAPER we have emphasized the importance of the monthly periods in woman with regard to various clinical phenomena, such as mental irritability, pulmonary edema, cardiac arrhythmias, gastrointestinal dysfunction, articular symptoms in rheumatoid arthritis, various dermatologic disorders, tetany, Addison's disease, bronchial asthma, and so on.[1] This periodicity is closely connected with the premenstrual phase of the menstrual cycle, and some authors have referred to the mental affection as "premenstrual tension." An investigation of the differential white count during the period was suggested by us in 1945, but abandoned after the appearance of the important paper of Davis and Hulit[2] on the changes in circulating eosinophils during the menstrual cycle.

As far as the central nervous system is concerned, the occurrence of epileptic seizures in close connection with the periods represents a well-known phenomenon which will not be referred to further. The same is true of migraine and myasthenia gravis. It has been suggested by Froin, Sven Ingvar, and Ehrenberg that there is an increased incidence of the occurrence of subarachnoid hemorrhage during the menstrual periods.[3] There are, however, some other disorders which are apt to present the same monthly periodicity: multiple sclerosis, Takayashu's disease, arteriovenous aneurysms, and meningiomas.

Multiple sclerosis is, in Sweden, one of the most common organic diseases of the nervous system, if the vascular lesions are excluded. It is generally estimated that some 7,000 persons in Sweden (with seven million inhabitants) are afflicted with this disease. Since it is likely to involve persons still in the age of fertility, we have ample experience of its behavior in young women. More often than not one may witness a considerable deterioration of the disease in the premenstrual and early menstrual phase and a corresponding amelioration afterwards. This peculiar rhythm may be registered, for instance, with regard to the gait, degree of nystagmus, speech, and acuity of vision if the optic nerves are involved.

Pulseless disease, or the syndrome of Takayashu, has recently been dealt with in another paper.[4] Attention was called to the important observations of Kouretas and Djakos regarding a premenstrual accentuation of the various symptoms, particularly the increased sensi-

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tivity of the carotid sinus reflex before and during the periods. The practical consequence is that patients with this disorder should be advised to remain in bed during the week concerned.

Arteriovenous aneurysms of the brain are observed most frequently in males (three out of four). In one young woman, observed by us several years ago, the symptoms were, as usually is the case, confined to epileptic seizures. Also, in this case, there was a marked periodicity, with the attacks occurring most frequently during the premenstrual phase. It may be a wise rule to increase the dosage of sedatives (phenobarbital, and so on), during the week preceding menstruation; this is also the case with epilepsy where no underlying lesion is to be identified. A few years ago we had the opportunity to observe a woman who died at the age of 64. Since the age of seven she had noticed a pulsating tumor in the right frontal region. At first it was rather small; in 1919 a sketch was made, at which time the tumor was the size of a hen's egg (figure 1). A photograph made 27 years later shows evidence of marked enlargement (figure 2). In 1951 she was admitted with severe cardiac decompensation, from which she eventually died. When questioned about the behavior of her pulsating tumor in the frontal region she was very positive about two facts: that it had increased in size and tension and pulsation before each period, returning afterwards to its original condition; and that it had, to some extent, done so also during her 10 pregnancies. The tumor was found to represent an entangled arteriovenous aneurysm, where the afferent arteries were supplied not only by the external carotid (to some extent also by the left external carotid), but also by the ophthalmic branch of the right internal carotid; the contribution from this source had the caliber of a pencil. This case seems particularly instructive since it deals with a lesion, visible externally and thus able to be observed by the patient herself. The cardiac insufficiency was obviously due to the increased load on the heart from the venous flow through the aneurysm. At necropsy valvular system and coronary arteries were

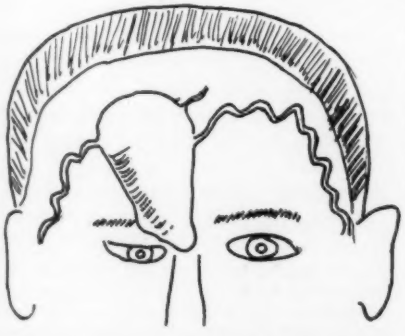

FIG. 1. Arteriovenous aneurysm of the forehead. Sketch made in 1919, when the patient was 32 years of age.

FIG. 2. Arteriovenous aneurysm some 27 years later (in 1946). Five years later (1951) it had extended still more.

entirely normal.

With regard to the meningiomas there are two important observations regarding sex incidence. On the one hand, this tumor is more common in women, and this is particularly so for certain localizations, such as the sphenoid ridge and the spinal canal. On the other hand, it is an old observation that this tumor is apt to become accelerated by pregnancy. We have made some observations which suggest a periodicity closely following the menstrual cycle. Thus, in one female, aged 47, mother of two children, headaches had been present during the previous 12 years, always worse before the onset of menstruation. For the last six years there had been attacks of syncope about four times a year, and these attacks always occurred a few days to one week before the onset of the menstrual period. She was found to present a large parasagittal meningioma, derived from the bregma region. In another woman, aged 52, attacks of headaches and lack of ability to concentrate were noted during the previous six months, always worse at the time of menstruation. This patient was found to have a parasagittal meningioma in the parieto-occipital border region. Hence it would appear that monthly periodicity may also become projected in the symptomatology of these tumors. No similar behavior has as yet been noticed as far as the gliomas are concerned, but attention will have to be focused on this matter in the future.

It is obvious that this monthly periodicity is a matter concerning only women. Yet, the author has had the opportunity to make some very strange observations in men. Thus one man, aged 68, maintained that he had suffered from severe stuttering since his youth. He had become a teacher and was required to deliver speeches and attend meetings where much speaking was required. As the years went by the stuttering improved, but reappeared with such periodicity that he kept a record in his diary. It became evident that the periods of stuttering always appeared during the week following full moon. He expressed the belief that self-suggestion was out of the question, since he did not discover the correspondence between the monthly cycle and the stuttering until several years later. It is impossible in such a case entirely to deny a "lunatic" influence, although all due criticism ought to be exerted against such phenomena.

SUMMARY AND CONCLUSIONS

Attention is called to the relationship between the menstrual cycle in women and various disorders of the central nervous system. The proneness of mental irritability, epilepsy, migraine, and myasthenia gravis to be particularly pronounced during the premenstrual phase is recalled. Other disorders where the same phenomena may be registered are multiple sclerosis, pulseless disease, arteriovenous aneurysms of the head, and meningiomas. The question whether a corresponding phenomenon may be met in men is touched upon briefly.

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CLINICAL PATHOLOGIC CONFERENCE

E. P. Richardson, Jr., M.D. Section Editor

Presented by *Thomas W. Farmer, M.D. and Margaret C. Swanton, M.D.*

PRESENTATION OF CASE

A 17 year old Negro student was admitted to the North Carolina Memorial Hospital, Chapel Hill, North Carolina on August 25, 1954 with the chief complaints of headache of one month's duration and of weakness of the left arm and leg of three days' duration.

The history on admission was obtained from the patient and was considered of questionable reliability due to the patient's drowsiness. The patient stated that he had been perfectly well until one month prior to admission. At this time he first developed a dull, constant right parietal and frontal headache. This was associated with pain behind both eyes and pain on movement of his eyes. The constant headache persisted. One week prior to admission he first noted increasing lethargy. Three days before admission he noted marked weakness of his left arm and leg associated with altered sensation of the left arm and leg.

There was no history of antecedent fever, earache, or drainage from either ear. There was no known head injury. The past history was not adequately obtained due to the patient's clinical condition.

Physical examination showed the following: Temperature 99.4° F. (rectally); pulse 86; respirations 20; blood pressure 140/75; weight 140 pounds. The patient was a well developed, well nourished Negro who complained of headache and pain behind both eyes. He was well oriented and cooperative but quite drowsy. The sensorium was clouded with a fluctuating level of awareness. There were no skin lesions. Examination of the skull revealed slight tenderness over the frontal regions bilaterally. No bruit was heard on auscultation of the skull. Examination of the eyes, ears, nose, and throat revealed no significant findings. The heart was of normal size and there was a grade I systolic murmur at the apex. The lung fields were clear to percussion and auscultation. There were no abdominal masses and no abdominal tenderness.

Neurologic examination revealed the following: *Cranial nerves*: The patient was able to recognize the odor of tobacco. The right pupil was very slightly larger than the left pupil. Both pupils reacted to light. Funduscopic examination revealed normal disks and normal retinas. The extraocular movements were normal. The visual fields were normal on confrontation. There was a left lower facial weakness. The palate moved normally, and the tongue was protruded in the midline. *Motor system*: There was paralysis of the left arm and leg with more complete involvement of the leg than of the arm. Sensory examination revealed decreased sensation to pinprick, light touch, and position sense in the left arm and leg. Reflex examination revealed that the deep tendon reflexes in the left arm and leg were more active than those on the right. The right abdominal reflex was more active than the left abdominal reflex. The plantar response was extensor on the left and flexor on the right.

Laboratory data: The urinalysis revealed a

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specific gravity of 1.025; albumin, sugar, and microscopic examinations were negative. Blood hematocrit was 45; white blood count was 6,400, with 73 per cent polymorphonuclear leukocytes, 26 per cent lymphocytes, and 1 per cent monocytes. A sickle cell preparation was negative. A lumbar puncture revealed an initial pressure of 200 mm. of water. The final pressure was 100 mm. Six cc. of clear colorless fluid was removed. The fluid contained no red or white blood cells. The spinal fluid protein was 25 mg. per cent. The spinal fluid sugar was 61 mg. per cent. Simultaneous blood sugar was 90 mg. per cent. The colloidal gold curve was 1111000000. Blood and spinal fluid serologic tests were negative.

Radiologic studies revealed an essentially normal chest and skull. No evidence of mastoiditis was seen. There was maxillary sinusitis, bilateral, greater on right.

Course in hospital: During the first day in the hospital the patient's level of awareness changed from that of mild somnolence to the point that the patient was difficult to arouse. He was seen by the neurosurgical service on the day of admission, and on the day following admission a ventriculogram was done. These films revealed that the bodies of the lateral ventricles were shifted to the left approximately 5 mm. (figures 1 and 2). There was no significant dilatation of the ventricles and no localized abnormality of the contour of the body. The third ventricle was also shifted, and this shift was greater in the superior than in the inferior portion of the third ventricle. The aqueduct and fourth ventricle were not demonstrated. The radiologic impression was that of a shift of the ventricular system to the left without any localized compression on the right, which is consistent with a mass lesion in the right convexity, probably soft in nature. Ventriculography was followed by a right temporoparietal craniotomy. Approximately six hours after surgical exploration the patient expired.

DIFFERENTIAL DIAGNOSIS

DR. THOMAS W. FARMER (Neurologist): At hospital admission this patient presented a subacute onset of a progressive illness characterized by a one-month history of headache, a one-week history of lethargy, and a three-day history of weakness of the left arm and leg. After admission the patient's state of awareness progressed from lethargy to stupor. The neurologic signs clearly indicated a pathologic process involving the right cerebral hemisphere in the posterior frontal and parietal areas. This boy was 17 years old, he was normotensive, he was not obese, and the laboratory studies showed no evidence of diabetes mellitus. The slight enlargement of the right pupil indicated possible pressure on the right third nerve secondary to edema of the right cerebral hemisphere. The observation that the left leg was more severely involved than the left arm suggested the possibility that the lesion in the right hemisphere was placed medially. Thus, the lateralization and localization of the lesion can be determined with some certainty from the clinical examination. The lesion is in the right posterior frontal and right parietal lobes.

The difficult problem in this patient is the determination of the etiology of this lesion. The spinal fluid examination revealed an initial pressure of 200 mm. of spinal fluid with a protein of 25 mg. per cent. Ventriculography (figures 1 and 2) revealed a shift of 5 mm. to the left of the bodies of the lateral ventricles and a shift of the third ventricle to the left. Thus, there was evidence of a space occupying lesion. The possible etiologies to be considered are the following:

1. Cerebral neoplasm, either a rapidly growing glioblastoma or a metastatic neoplasm. The studies done on this patient during his first day in the hospital revealed no site for an extracerebral primary neoplasm. The progressive course and the findings on ventriculography are consistent with glioblastoma. However, there was no localized compression of the right lateral ventricle and the diffuse manner in which the right lateral and third ventricle were displaced suggests the possibility of a nonneoplastic edematous process or possibly a subdural hematoma.

2. Subdural hematoma. There was no history of head injury. The rapidly progressive course and the severe neurologic deficit with a relatively slight shift of the ventricular system make this diagnosis un-

FIG. 1 and 2. Ventriculograms made August 26, 1954.

likely.

3. Brain abscess. There was no history of ear or sinus infection, no pleuropulmonary disease, no evidence of congenital heart disease, and no site for a primary infection elsewhere in the body. The cerebrospinal fluid revealed no increase in cells or protein. The possibility of abscess cannot be completely excluded but is considered very unlikely.

4. Meningovascular neurosyphilis. This has been excluded by the serologic studies.

5. Aneurysm. Intracerebral bleeding into the right hemisphere from leakage of an aneurysm is a possibility. However, there was no subarachnoid bleeding. This diagnosis seems unlikely.

6. Cerebral thrombosis. Large arterial occlusions may occasionally be associated with increased intracranial pressure, papilledema, and rarely with slight shift of the ventricular system. If this is a vascular lesion it is in the distribution of the right internal carotid system and might be due to thrombosis either in the right internal carotid artery or in the right middle and anterior cerebral arteries. If this is a vascular lesion, the etiology is obscure. There is no evidence in the patient's protocol to suggest the possibility of periarteritis nodosa, lupus erythematosus, thromboangiitis, purpura, or sickle-cell anemia. Cerebral arteriosclerosis of severe degree rarely occurs in adolescence. Ford[1] has described the pathologic findings in a child who died as the result of an infantile hemiplegia. This was a three years and 11 months old boy who developed stupor and a left hemiplegia followed by death on the third hospital day. At postmortem examination a thrombus was found in the right middle cerebral artery. The cause of the changes in the cerebral arteries remained obscure. Ford also states with reference to infantile hemiplegia that "in the early stages of the illness the affected hemisphere may be so swollen that ventriculographic study may suggest brain tumor. Later, of course, atrophy becomes evident." Berlin and associates[2] have recently reported 13 cases of acute cerebral vascular lesions in young adults of 18 to 34 years of age. Thrombosis in these cases was "attributed to occlusive vascular disease, such as arteriosclerosis."

The history and course of this boy's illness are consistent with either a rapidly growing infiltrating neoplasm or a relatively rare arterial occlusion associated with cerebral edema and resultant diffuse ventricular shift.

DR. C. C. SMITH (Resident): I saw this patient on admission. The neurologic examination was as described. I felt that the right eardrum was pink and that there was skull tenderness in the right temporal and frontal regions. For this reason I felt that a brain abscess in the right cerebral hemisphere was a likely diagnosis.

DR. ERNEST WOOD (Radiologist): The ventriculographic findings are consistent with a soft lesion in the high, right, midfrontal, and parietal regions. The possibility of a temporal lobe abscess cannot be completely excluded.

DR. GORDON DUGGER (Neurosurgeon): I reviewed the ventriculograms very carefully with the radiologist prior to surgery. It was noted that there was complete filling of the right ventricle with no evidence of a filling defect or deformity of the ventricular contour. The ventricular shift was 5 mm. The possibility of a primary vascular disorder with associated edema was considered. However, in view of the definite ventricular shift, a craniotomy was performed. A right temporoparietal craniotomy exposed the middle and posterior thirds of the right superior temporal convolution, as well as the right central and precentral regions. The surface of the cortex was diffusely hyperemic. The gyri were of normal width. The cortex was normal to palpation. Needle biopsies were taken. These revealed no neoplastic tissue. The report on the first tissue was early ischemic change in the temporal and inferior frontal cerebrum.

During the operative procedure the brain pressure gradually increased, and at the time of closure of the dura the tension was fairly great. Complete dural closure was effected by decompression. The patient was returned to the ward in fairly good condition. He expired six hours later of respiratory failure.

PATHOLOGIC DISCUSSION

DR. MARGARET C. SWANTON (Pathologist): Autopsy of this well developed young Negro male revealed few abnormalities except for the intracranial lesions. The relatively few extracranial lesions can be summarized briefly, along with some of the negative findings of significance in relation to the primary disease process. Early bilateral arcus senilis was present. The thymus was prominent, as is usual at puberty, with a parathyroid gland imbedded in it. The thyroid was normal. There were moderate pulmonary congestion and edema and an acute tracheitis. The aorta had a few scattered yellow streaks in the intima, representing early atherosclerosis. The heart was of normal size (weight 240 gm.), with no evidence of valvular or vascular lesions. No gross or microscopic abnormalities were seen in the kidneys.

Bilateral scalp incisions overlay posterior parietal burr holes, and a 25 cm. right frontotemporal craniotomy incision was present over a bone flap sutured in place. A moderate amount of subgaleal hemorrhage was present, but epidural hemorrhage was small and subarachnoid hemorrhage slight at the operative site, where only needle biopsies had been taken. No other areas of hemorrhage were evident when the brain was removed. Dural sinuses contained no thrombi.

The brain weighed 1,570 gm. and showed moderate flattening of gyri and proportional narrowing of sulci. Leptomeninges were thin and transparent. The most striking change consisted of a definite softness, with less sharp definition of gyri, of the entire right frontal lobe, both medially and laterally. This was clearly palpable posteriorly as far as the central sulcus, and to a less marked degree posterior to the sulcus. The uncus appeared slightly broader on the right side than on the left, but showed no groove from compression against the edge of the tentorium.

The circle of Willis, with its arterial branches, was dissected *en bloc* from the brain. There were no gross lesions in the adventitia of any of the vessels. No congenital anomalies were present. The basilar artery showed a slight increase in opacity of its wall. In the distal segments of the

internal carotid arteries, thickening of the wall was more marked and associated with decreased pliability. Similar changes were much more prominent in the main stems of middle cerebral and proximal segments of anterior cerebral arteries. Their lumina showed variable degrees of narrowing, severe in the middle cerebral arteries, where several soft, yellow, eccentrically located intimal placques were identifiable. These lesions were most marked in the right middle cerebral artery (see cross section, figure 4, taken from artery seen *in situ* on the circle of Willis in figure 3 at site of incision to left of arrow). In the course of a few millimeters there was a transition from the involved arterial segments to normal arterial walls distally, and branches of the arteries were free of lesions. On the right side, the proximal 7 mm. of the middle cerebral and

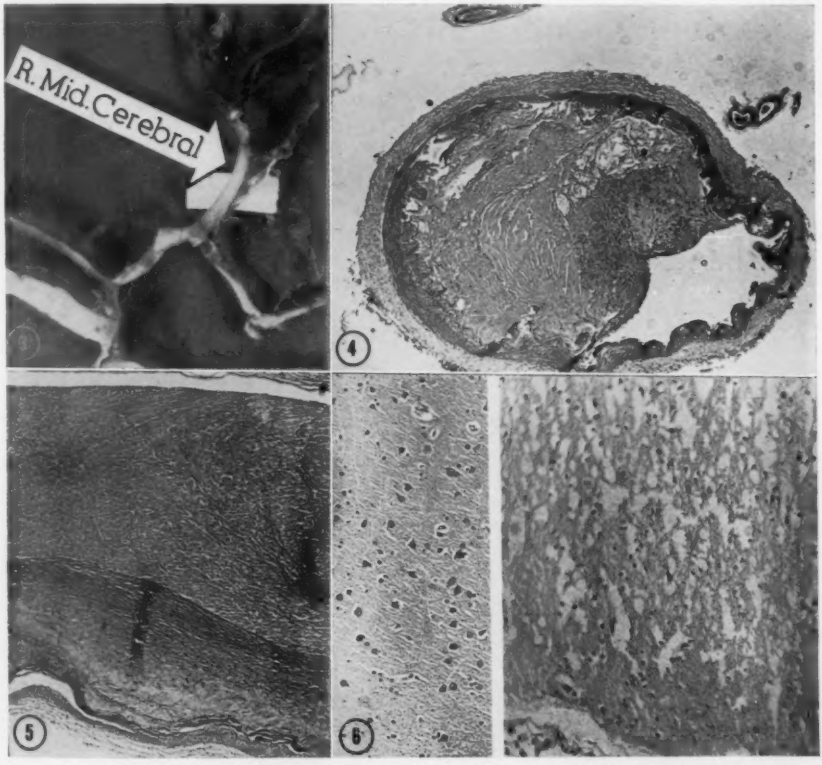

FIG. 3. Right half of circle of Willis. Basilar artery in lower left corner, anterior cerebral in lower right, with thrombus occluding lumen proximally. Incision in middle cerebral artery through atherosclerotic placque distal to thrombosis.

FIG. 4. Cross section of right middle cerebral artery through yellow, eccentric atherosclerotic placque, distal to thrombosis.

FIG. 5. Longitudinal section of proximal right middle cerebral artery, with moderate atherosclerosis (lower part of field) and thrombus occluding lumen (upper part of field).

FIG. 6. Right frontal cerebral cortex with early ischemic necrosis; left frontal cortex for comparison.

the proximal 2 mm. of the anterior cerebral artery were distended, rigid, and firm, with complete occlusion of their lumina by a firm, dry thrombus, continuous from one vessel into the other (figures 3 and 5).

Histologically these vascular lesions were characteristic of atherosclerosis. The milder changes were increased intimal fibrous tissue, with minimal amounts of interstitial lipid deposition and reduplication of internal elastic lamellae (figure 5). The thick intimal placques consisted of fibrous and elastic tissue, with both interstitial lipids and "foam cells" (figure 4). The only inflammatory reaction in the vessels was in and adjacent to a small, superficial area of necrosis of the intima in one of the placques at the site of middle cerebral thrombosis. In this same section was a small area of fresh hemorrhage into the thick intima. These findings suggest that the series of events proposed by Paterson[3] as precursors to thrombosis in atherosclerotic arteries did in fact occur in this artery, that is, intimal capillary hemorrhage in a placque, leading to superficial necrosis, with or without rupture of the intima. Degenerative changes or scarring of the media were not present. Sections of the thrombosed vessels showed only a relatively recent thrombus, with earliest peripheral fibroblastic proliferation in some areas. This is consistent with a thrombosis of several days' duration, but not with a partial thrombosis dating back to the onset of the patient's illness. Paterson suggests that the transient prodromata of thrombosis may be due to vasomotor reactions resulting from early intimal capillary hemorrhage.

Coronal sections of the brain confirmed the softening of the entire right frontal lobe, with blurring of gray-white junctions, and without significant discoloration. There was no liquefaction of the tissue. Less marked softening involved the anterior parietal lobe, island of Reil, and anterior corpus striatum on the right. A slight shift of midline structures to the left was still evident. The histologic changes were those of early ischemic necrosis of cerebral tissue (figure 6), complete in sections of frontal cerebrum, and patchy in the corpus striatum. Frontal leptomeninges showed congestion of vessels, proliferation of arachnoid cells, and mild neutrophilic infiltration. Minimal leukocytic and no glial cell reaction was present in the brain tissue. In sections from other parts of the brain there were neuronal alterations in a dentate nucleus, in the Purkinje cell and granular layers of the cerebellum, and in the pyramidal layer of the right uncus, consistent with terminal hypoxia.

In summary, the major anatomic diagnoses are: Atherosclerosis, severe, of internal carotid, middle and anterior cerebral arteries, and mild, of aorta. Thrombosis, recent, right middle and anterior cerebral arteries. Encephalomalacia, recent, right frontal and anterior parietal cerebrum and corpus striatum.

Question, from the audience: If this was ischemic infarction resulting from complete occlusion of these arteries, how do you account for the observation at operation that the surface of the cortex was diffusely hyperemic?

Two factors can account for this apparent contradiction. One is backflow of blood into superficial veins, facilitated by operative intervention that reduced the external pressure on these vessels resulting from the edema that accompanies early infarction. Secondly, there are meningeal arterial anastomoses between branches of the various cerebral arteries, that is, right and left anterior cerebral arteries, middle and posterior cerebral arteries, to use examples relevant to this case. Reduction of intracranial pressure, plus the normal reaction of vessels to operative manipulation, would increase the rate of flow in these anastomoses. In some cases the collateral circulation via these channels can be of sufficient magnitude to produce clinically significant alteration in the amount of damage resulting from occlusion of a major cerebral artery, as has been well demonstrated by Vander Eecken and Adams.[4] In this case the left anterior cerebral artery was a weak crutch to help sup-

port the right frontal lobe, since its lumen was narrowed by atherosclerosis. As a matter of fact, the right posterior cerebral artery may have played a minor role here, because the encephalomalacia did not extend as far posteriorly as the usual area of middle cerebral artery supply.

In this case we have severe atherosclerosis, quite strikingly localized, leading to fatal thrombosis, in a patient well below the average age of incidence of such lesions. Furthermore, none of the systemic diseases are present which have been considered as predisposing to early atherosclerosis: hypertension (essential or secondary to chronic renal disease), diabetes, or rheumatic heart disease.[5]

It is becoming increasingly apparent that atherosclerosis is a metabolic disease with onset early in life. An analysis of aortic lesions in 300 unselected autopsies revealed the earliest occurrence of atherosclerotic lesions at one and one-half years, with no person beyond the age of seven entirely free of early lesions.[6]

Several excellent studies of coronary arterial disease have emphasized its incidence in persons below the age of 40, such as Moritz's[7] report of about 1,000 cases of sudden and unexpected deaths in young soldiers, over 20 per cent of which were due to coronary atherosclerosis. It is difficult to find in the literature any significant number of proved cases of severe cerebral atherosclerosis with or without thrombosis in younger age groups, particularly in the age group of our case. Dr. Farmer has mentioned Ford's[1] case of infantile hemiplegia due to thrombosis of an atherosclerotic middle cerebral artery. Irish[8] reports a case of bilateral internal carotid artery thrombosis at the age of two years, the only one out of 40 cases of cerebrovascular accidents occurring before the age of 20 that was due to arterial thrombosis. In 740 cases of apoplexy seen at Johns Hopkins Hospital, Thomas[9] reports 25 in the second decade (the decade of lowest incidence of apoplexy), of which three might, on clinical grounds, be on the basis of thrombosis complicating primary vascular disease. The recent report of Berlin[2] on 13 cases of cerebral thrombosis in persons under 40, including one at age 18 and three others under the age of 25, deals with cases in which embolism, hemorrhage, and many fairly specific types of vascular disease have been ruled out on clinical grounds, leaving thrombosis based on "occlusive vascular disease such as arteriosclerosis" as the most likely diagnosis. Four showed arteriographic evidence of narrowed or occluded arteries, one had biopsy evidence of encephalomalacia, and this last case plus three others had later evidence on air studies of focal atrophy.

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DIAGNOSTIC NOTE

Head Turning

A Maneuver to Elicit the Neurologic Signs of Hoarseness and Dysphagia

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HOARSENESS AND SWALLOWING DIFFICULTY may appear only when the head is rotated to one side. In the examination of neurologic patients, the simple maneuver of turning the head may elicit dysfunction of the pharynx and larynx not present when the patient is facing straight ahead.

Two patients and 20 control subjects have been examined.

Case 1.—A 19 year old man suffered a head injury with unconsciousness in 1952. Residuals of this accident included deafness in the right ear, mild dysphagia, and mild hoarseness. Neurologic examination showed decreased bone and air conduction on the right, and slight weakness of elevation of the palate on the right. With the head turned straight forward there was no hoarseness or dysphagia drinking water. The patient did report, however, that his voice became much hoarser when he turned his head to the right. When he slept on his right side at night, he was awakened by coughing.

When the patient was examined with his head turned to the right, his voice became low pitched and extremely hoarse, so that he could hardly be understood. In this position, also, marked dysphagia was observed on drinking water, with coughing and regurgitation of fluids through the nose.

Indirect laryngoscopy revealed normal position of the vocal cords, but when the head was turned to the right the vocal cords separated and could not be approximated with phonation. Fluoroscopy done while the patient was drinking a thin barium mixture showed a large sacculation of the upper esophagus on the right side when he drank the liquid with his head turned to that side. Esophagrams with the head forward or turned to the left side were normal.

Case 2.—A 24 year old white man suffered an attack of bulbar poliomyelitis in 1953, requiring respirator treatment. As residuals he reported slight dysphagia for solid food and slight hoarseness. Neurologic examination revealed slight weakness of elevation of the left palate and mild weakness and atrophy of both shoulders. He reported, however, that his dysphagia was worse when he turned his head to the right, and that his voice was "different" when his head was turned to that side.

Examination with his head straight ahead revealed no hoarseness. With his head turned to the right his voice became nasal, low-pitched, and hoarse. There was no dsyphagia with the head turned to the front. When the patient turned his head to the right and attempted to drink water, he was unable to swallow, choked, and began coughing.

Indirect laryngoscopy revealed normal vocal cords, but when his head was turned to the right the vocal cords were separated and could not be approximated by phonation.

CONTROL STUDIES

Twenty persons without neurologic disease were studied. No person demonstrat-

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ed hoarseness or dysphagia with his head turned to either side. In four of these normal subjects indirect laryngoscopy revealed no separation of the vocal cords with the head turned to either side. In four subjects fluoroscopy showed no sacculation of the upper esophagus after swallowing thin barium with the head turned to either side.

COMMENT

In the two patients presented here the neurologic examination was within normal limits, except for slight weakness of elevation of one side of the palate. Special questioning revealed a history of hoarseness and dysphagia when the head was turned to one side. On neurologic examination with the head straight ahead, the voice was normal and there was no difficulty swallowing water. However, turning of the head to one side revealed marked hoarseness and dysphagia. Indirect laryngoscopy of the two subjects showed that head turning produced separation of the vocal cords. In one subject, an esophagram demonstrated marked sacculation of the upper esophagus only when the head was turned to one side. In 20 normal persons head turning produced no abnormality of voice or swallowing function.

The dysfunction of the vocal cords and pharynx produced by head turning in these patients with lesions of the motor nuclei or peripheral motor fibers of the vagus nerve are probably mechanical effects of weak muscles in the pharynx and larynx. Head turning seems to exert a torsion effect on the voice box and pharynx which, if muscular weakness is present in the larynx or pharynx, may produce hoarseness or dysphagia or both. The abnormal sacculation of the upper esophagus is probably due to weakness of the lower pharyngeal constrictors.

Head turning both toward and away from the side of the weak elevators of the palate has evoked hoarseness and dysphagia. Therefore, while this maneuver may reveal unrecognized weakness of palate or pharyngeal muscles, no conclusion as to the side of the muscle weakness is justified from this method of testing.

It is suggested that voice and swallowing function be tested with the head turned to each side, as well as straight ahead. Such testing, with appropriate interpretation of the history, may reveal lesions of the motor nuclei and peripheral motor fibers of the vagus nerve not recognized on the conventional neurologic examination.

CONCLUSION

In patients with slight or moderate weakness of the vocal cords and pharynx, turning of the head to either side may produce hoarseness and dysphagia not observed when voice and swallowing function are examined with the head straight forward.

CASE REPORT

Herniation of the Medulla Oblongata Causing Death in Meningococcal Meningitis

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IN CIVILIAN COMMUNITIES, meningococcal infections occur sporadically, with occasional small outbreaks. At an army basic training center, however, infections caused by *Neisseria meningitidis* are so common during the months of October to June that they present a constant problem. Not only may these infections be explosive and disastrous by their very nature, but also the premonitory features, especially with meningitis, simulate many nonspecific respiratory infections which are relatively innocuous. These similarities delay the diagnosis and complicate the problem further.

During the interval between January 1953 and July 1954, there were 76 cases of meningococcal infections treated in the U. S. Army Hospital at Fort Dix, New Jersey. Thirteen patients had septicemia, with one death due to bilateral adrenal hemorrhage (Waterhouse-Friderichsen syndrome). Of the 63 cases of meningitis, four died. Two died of Waterhouse-Friderichsen syndrome, and two died as a result of herniation of the medulla oblongata through the foramen magnum. This paper represents a report of these last two cases.

CASE REPORTS

Case 1.—A 19 year old basic trainee was admitted to the hospital on November 6, 1953. He had visited his dispensary on November 5 because of a "cold" for a day and was found to have a nonspecific pharyngitis with normal temperature. He received symptomatic therapy and was restricted to quarters. Although he was present at reveille the next morning, he collapsed a short time later and immediately was hospitalized by ambulance in an unconscious state.

Physical examination revealed a well-developed and well-nourished white semicomatose man with rectal temperature 102° F. Blood pressure was 140/70, pulse 80, and respirations 30. Breathing was stertorous but regular. The patient had carpopedal spasms bilaterally. He resisted stimuli by withdrawal. There were numerous petechiae on the trunk and several macular, dime-sized lesions on the legs. The eyeballs deviated downward; the right pupil was slightly larger than the left, but neither reacted to light. A few minutes later the pupils were pinpoint. Funduscopic examination could not be done; mouth and pharynx could not be examined because of marked trismus. The neck was rigid; Brudzinski's sign was present. There were rhonchi throughout both lungs. The heart and abdomen were normal. There was no peripheral edema or lymphadenopathy.

Because of the clinical diagnosis of meningococcal meningitis, a lumbar puncture was performed immediately. The fluid was cloudy yellow under markedly elevated pressure, although manometric measurements were not done. Laboratory examination of the fluid was as follows: cell count was 22,500 with 100 per cent neutrophils; smear revealed many gram-negative intracellular biscuit-shaped diplococci; protein was 400 mg. per 100 cc.; chlorides were 570 mg. per 100 cc.; and sugar was 32 mg. per 100 cc. Culture of the fluid under carbon dioxide subsequently yielded *Neisseria meningitidis*, type II-A. A blood culture drawn upon admission failed to reveal any growth at any time.

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The patient was immediately given one million units of aqueous penicillin intravenously, followed by intramuscular aqueous penicillin one million units every two hours. Intravenous therapy included 500 cc. of ⅙ molar lactate containing 2.5 gm. of sodium sulfadiazine given in 30 minutes. An infusion of 5 per cent glucose and saline with 2.5 gm. of sodium sulfadiazine was given over the next three hours.

During the first few hours in the hospital fresh petechiae continued to appear. The patient remained in a restless coma, but appeared to improve slightly three hours after treatment was started. At this time he was slightly more responsive. However, minutes later he went into a deep coma with irregular respirations, cyanosis, and convulsive seizures. At the same time he developed extensor rigidity. Five hours after admission the patient began to develop tracheal rales and suction was necessary. The cyanosis increased and respirations ceased. The pupils became dilated and fixed to light, and funduscopic examination revealed slight choking of the disks bilaterally. An endotracheal tube was passed, but the patient could not be resuscitated, in spite of continuous suction, artificial respiration, intravenous coramine, and intracardiac adrenalin. Death occurred five and a half hours after admission and less than two days after the onset of his disease. The clinical diagnosis was meningococcic meningitis, with death due to failure of the vital medullary centers.

At postmortem examination performed on November 6, 1953, the positive findings were: petechiae and purpura on the skin of the trunk and extremities, left lower lobe confluent lobular pneumonia, congenital cysts of both kidneys, diffuse purulent and hemorrhagic meningococcal meningoencephalitis, cerebral edema, and medullary compression. The brain weighed 1,400 gm. and exhibited purulent material over its entire surface especially over the vertex and base. The surface of the right cerebral hemisphere showed thin hemorrhage mixed with the purulent exudate. The brain was securely wedged in the posterior fossa so that a pressure cone was present over the inferior surface of the cerebellum. Microscopic examination of the brain revealed polymorphonuclear infiltration and hyperemia of the arachnoid and pia. The underlying cortex of the brain in some areas showed foci of hemorrhage with polymorphonuclear infiltration. Elsewhere there was edema, as evidenced by widening of the Virchow-Robin spaces and by increased vacuoles of the white substance of the brain. In the region of the compression, sections of the medulla revealed perivascular hemorrhage.

Case 2.—A 20 year old basic trainee was admitted to the U. S. Army Hospital, Fort Dix, New Jersey, on May 11, 1954. The past medical history revealed that the patient had had scarlet fever in addition to the usual childhood diseases. He also had a depressed skull fracture at about age 15; surgical therapy was completely satisfactory without sequelae.

The patient had a "head cold" on May 4, 1954. On May 11 he developed a sore throat followed by chills and fever. Examination at that time revealed a temperature of 103° F., moderate inflammation of the pharynx, and normal heart and lungs; he was admitted to the respiratory disease ward. At the time his morning temperature was taken on May 12, the patient bit off the end of the thermometer and swallowed it. He was noted to be extremely irrational, thrashing about in bed with intermittent twitching seizures. Within a matter of several minutes he became comatose. At this time the temperature was 103° F., and blood pressure was 120/65. He was cyanotic, completely flaccid, and without reflexes. The neck could be flexed. The pupils were fixed with the left one approximately 7 mm. in diameter and the right one 4 mm.; funduscopic examination was normal. He responded to deep pressure pain with marked spasm of both upper extremities; there was a left flexor response on stroking the plantar arch of the foot. There were a few petechiae on the dorsum of the right foot.

The admission white cell count was 20,000, with 84 per cent neutrophils; hemoglobin was 11.5 gm. The next morning the white count was 38,950, with 89 per cent neutrophils, and the hemoglobin was 13 gm. The urinalysis revealed a trace of albumin with a few red cells. Chest x-ray revealed irregular areas of diminished radiance consistent with pneumonitis at the right base. A spinal puncture was done. Spinal fluid pressure apparently was normal, although manometric testing was not done. The spinal fluid was cloudy with 4,250 white cells (90 per cent neutrophils), sugar was 42 mg. per 100 cc., and protein was normal. The direct smear of the spinal fluid was negative, but culture two days later revealed a gram-negative intracellular diplococcus, type II-A. Throat culture revealed normal flora with a slight increase of pneumococci but no meningococci.

Aqueous penicillin was given, one million units intravenously, and one million units intramuscularly every two hours. Gantrisin was given intravenously, 4 gm. in the first hour and 2 gm. every eight hours. Although the pulse and blood pressure were adequate and

the temperature began to fall, respirations became very irregular. Later in the morning of May 12 the patient's respirations improved as a result of intravenous caffeine and sodium benzoate. Pulse and blood pressure remained at satisfactory levels and the patient was a little bit more responsive to painful stimuli. This situation continued until early afternoon when the left pupil became smaller and the right pupil slightly larger; they still did not react to light. At about 9:30 p.m. the patient became apneic and intensely cyanotic when taken out of the oxygen tent. Blood pressure was 140/60, and the pulse was 160 per minute, of good quality. Artificial respiration, intravenous coramine, and oxygen by nasal catheter produced prompt improvement. Respirations remained very shallow, however. It became obvious that the vital centers in the medulla were completely paralyzed, probably due to a pressure cone. Because of his difficulty with respiratory movements, the patient was placed in a Drinker respirator with prompt improvement of the skin color. Pulse and heart sounds remained good. He received 300 mg. cortisone intramuscularly and adrenocortical extract, 10 cc. every half hour. Additionally, norepinephrine (4 mg. per liter) was given by constant infusion. Penicillin and Gantrisin dosages were continued as before. Caffeine and sodium benzoate were given every two hours for stimulating effect.

Throughout the following day the patient's condition was unchanged. He was maintained constantly in the respirator. Penicillin, Gantrisin, oxygen, norepinephrine, and adrenocortical extract were administered continuously. Then the urine output began to decrease rapidly, so that for the entire day of May 14 he voided only 175 cc. Repeated Gantrisin blood levels had ranged between 10 and 15 mg. per 100 cc. until he became oliguric, when the level went up to 35.5 mg. per 100 cc. During the night his pulse was imperceptible. This terminal state continued for another 24 hours until 9:30 p.m. on May 15 when the patient died. The clinical diagnosis was meningococcal meningitis with death caused by medullary paralysis due to a pressure cone.

Postmortem examination on May 16 revealed the following: old petechial and purpuric lesions on skin; bilateral pulmonary congestion and edema, bronchopneumonia right upper and right middle lobes, abscess of upper portion of right lower lobe; suppurative meningitis; and herniation of the cerebellar tonsils, with degeneration of the medulla. The entire surface of the brain was covered with yellowish white exudate. The medulla and portions of the cerebellum were wedged within the foramen magnum and the medulla was soft and partially necrotic. The cerebellar tonsils were attenuated, forming a pressure cone. Microscopically, there was polymorphonuclear invasion and hyperemia of the meninges. In some areas this process extended into the cortex. The compressed medulla showed evidence of cellular degeneration.

DISCUSSION

Of the infectious diseases encountered in the army, meningococcal infections are responsible for most of the deaths. The innocuous premonitory symptoms increase the mortality rate as evidenced by case 1. In case 2 the "head cold" probably was not a prodromal part of the disease. Although sulfadiazine and Gantrisin have been uniformly effective against the meningococcus, complications occur frequently enough to account for a mortality rate of 5 to 10 per cent. Energetic chemotherapy may be too late to stave off myocarditis, adrenal depletion, severe toxemia, or herniated medulla.

Daniels analyzed 300 fatal cases of meningococcal infection and found that a pressure cone was present in four.[1] This complication is fatal because the sensitive centers in the medulla cannot tolerate even slight or brief injury. After a matter of minutes the medullary depression may be irreversible, and the patient may die within three or four days.

In both of the patients discussed in this paper the cerebellar pressure cone may have been partially a result of the spinal punctures. In the first case, medullary depression occurred three hours after the puncture, and in the second case, about one and a half hours afterward. In the presence of an elevated cerebrospinal fluid pressure, a careless spinal puncture may initiate the process of herniation.[2] Certainly, the spinal puncture should be a careful one, pressure should be determined, the fluid should be removed cautiously, and Queckenstedt's maneuver should be eliminated.

SUMMARY

Two fatal cases of meningococcal meningitis with herniation of the medulla are presented and discussed. This complication is a fatal one in spite of the fact that the organism *Neisseria meningitidis* is susceptible to adequate doses of sulfa drugs and antibiotics. In some cases, herniation of the medulla oblongata may be as important as adrenal depletion or overwhelming septicemia in the mortality rate of meningococcal meningitis.

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■ We look upon this first work of Sir Charles Bell on the nervous system ("An Idea of a New Anatomy of the Brain") as an admirable production of the genius of this great physiologist. The idea of the distinction between the nervous elements employed in the different functions of the nervous system is there clearly and forcibly presented, and we may safely state that the greatest part of the recent progress of our knowledge of the nervous system, both in a practical and in a scientific point of view, has its source in this idea. There is another important thing in this little pamphlet; it is the result of Sir Charles Bell's experiments on the roots of the spinal nerves. He found, on a dying animal, that the irritation of the anterior roots caused muscular contractions, while there was no effect produced by the irritation of the posterior roots. Of course this experiment could not show what are the functions of these roots, but it was sufficient to prove that there is a notable difference between the anterior and the posterior roots.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Spontaneous Intraspinal Hemorrhage and Paraplegia Complicating Dicumarol Therapy

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PARAPLEGIA resulting from intraspinal hemorrhage is an unusual complication of anticoagulant therapy with dicumarol. It is not uncommon for a hemorrhagic state to develop in the course of therapy. Serious non-fatal complications are frequently encountered and deaths have been reported in several excellent reviews in the current literature.[1–4] Intracranial bleeding occurs and death is often due to cerebral hemorrhage.[1] Intraspinal hemorrhage and paraplegia following lumbar puncture have been reported in patients being treated with dicumarol.[5] A transient quadriplegia which occurred in a patient under treatment with this drug has recently been described by Arieff and Pyzik.[6] In this instance excessive amounts of dicumarol were administered. The patient recovered partially but a severe, incomplete, spastic paraplegia remained. The etiology of the paralysis was not verified by operation; hence the authors were unable to state with certainty whether the paraplegia resulted from intraspinal hemorrhage, embolism, or from some other cause.

It is the purpose of this report to describe an instance of paraplegia which developed as a complication of dicumarol therapy. The cause of the paraplegia, namely extensive epidural, subdural, and subarachnoid hemorrhages, was verified at the time of operation. To our knowledge, no similar case has been reported.

CASE REPORT

A 66 year old white man entered the University of Chicago Clinics on May 18, 1954 with a history of having suffered intermittent attacks of severe pain localized to the left precordium for five or six weeks prior to admission. Physical examination at that time was essentially within normal limits. An electrocardiogram revealed evidence suggestive of a posterior myocardial infarction. Dicumarol therapy was instituted and the daily dosage was adjusted so as to maintain the prothrombin time between 30 to 50 per cent.[6] On the eighth hospital day the patient experienced gross hematuria and epistasis. The prothrombin time had fallen to 14 per cent. The patient was given vitamin K_1 oxide, 50 mg. intravenously. There was prompt cessation of both hemorrhagic phenomena. He was thereafter maintained on dicumarol with no untoward effects, and discharged on the twenty-fourth hospital day with a prothrombin time of 54 per cent.

While at home the patient took dicumarol, 100 mg. and 150 mg. on alternating days. On June 21 the prothrombin time was 17 per cent. Dicumarol was withdrawn for three days. Subsequently he received 100 mg. and 50 mg. of the drug on alternating days. On July 1 the patient first noted onset of pain in the back of the neck, upper thorax, and in the low back, described as a dull, continuous ache. Associated with the pain was a sensation of weakness of both legs. On the morning of July 5 the pain in the thorax and back became excruciatingly severe and he noted radiation of the

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pain into both lower extremities. There was associated stiffness of the neck. The weakness of the legs became more pronounced. Because of the severity of the pain, the patient reentered the hospital on the evening of July 5.

Physical examination at this time revealed moderate, generalized weakness of both lower extremities but was otherwise normal.

The pain was so severe that the patient required large doses of morphine. On the morning of July 6 the weakness of the legs had progressed. Neurosurgical consultation was obtained on the afternoon of the same day. Examination at this time revealed a nearly complete paraplegia and urinary retention. There was minimal voluntary motion in the toes of both feet. Diminished tendon reflexes in both lower extremities were obtained only on reinforcement. There were no responses on testing the abdominal and plantar reflexes. Marked hypalgesia to the level of the dermatome of L 1 was found on the right, and patchy hypalgesia in the L 4, L 5, and S 1 dermatomes on the left. A diagnosis of intraspinal space-occupying lesion was made. Radiographs of the thoracic and lumbar spine were obtained and were normal. Later neurologic examination disclosed a complete absence of all tendon reflexes, and flaccid paraplegia except for feeble dorsi- and plantar flexion of the right great toe. There was an inconstant sensory level at approximately the first lumbar dermatome on the right.

Myelography and immediate surgery were advised, but because the prothrombin time was only 11 per cent these procedures were postponed. In the succeeding four hours the patient received 100 units of vitamin K_1 oxide intravenously and a transfusion of 500 cc. of whole blood. The prothrombin time was repeated and found to be 70 per cent. A myelogram was then attempted, but a satisfactory communication with the lumbar subarachnoid space could not be obtained. One cc. of Pantopaque was instilled and was shown by fluoroscopy to be in the epidural and subdural spaces. The procedure was therefore abandoned.

Reexamination at this time revealed that the feeble movements of the right great toe were still present, but there was a profound increase in the loss of all modalities of sensation on the right below the level of the eleventh thoracic dermatome. There were patchy areas of preserved sensation over the left lower extremity, without a definite sensory level.

Laminectomy of T 11 and 12 and L 1 was performed under local anesthesia. Upon removing the laminae, a layer of black, semicoagulated blood, 3 to 4 mm. in thickness, was encountered in the epidural space. The hematoma was localized more to the right of the midline and was confined to the T 12 and L 1 levels. After the clots were removed, pulsation of the dura was not observed. The origin of the hematoma was not discovered, except as a general oozing from small epidural veins.

The dura was opened and a considerable quantity of purple-red blood escaped under pressure from the subdural space. The arachnoid membrane over the spinal cord was purple-red in color, and similar dark bloody fluid was found in the subarachnoid space. After the blood in the subdural space had been thoroughly removed by irrigation and suction, normal pulsations of the cerebrospinal fluid returned.

The patient recovered rapidly from the operation. Within 48 hours voluntary movements had returned in both lower extremities. Rapid improvement occurred for the first ten days, but since then the patient's progress has been slow. At examination, 57 days after operation, all voluntary movements in the right lower extremity had returned but not in sufficient degree to permit him to stand without support. There was still considerable residual weakness of the left lower extremity, dorsiflexion of the foot, and severe flexion and extension of knee. The patient was unable to walk without assistance. Bladder control had not returned.

COMMENT

Immediate operative intervention is the treatment of choice for this complication. Unnecessary delay decreases the patient's chance of recovery. In this instance the laminectomy was necessarily delayed because of the low prothrombin time (11 per cent). The hazard of performing an operation under these conditions is apparent. Immediate intravenous administration of vitamin K_1 oxide and whole blood transfusion is mandatory.

At operation the extradural hemorrhage was observed to be confined to a limited area. The subdural hemorrhage, on the other hand, was more extensive. It would appear that the paraplegia was due to a

*The prothrombin time as it is used at this clinic is the control prothrombin time in seconds times 100, divided by the patient's prothrombin time, and expressed as a percentage. A prothrombin time of 50 per cent represents a prothrombin time twice the normal control. The figures 30 to 50 per cent are used as the therapeutic range.

combination of the two. The subarachnoid hemorrhage was generalized and accounted for the stiffness of the neck. Subarachnoid hemorrhage without focal neurologic signs is not an indication for operation.

The exact etiology of the hemorrhage was not determined in this case. It seems unlikely that alteration of the prothrombin activity by dicumarol was the only cause of the intraspinal bleeding. It is more probable that a vascular accident, asymptomatic or trivial — under other circumstances, initiated the syndrome in a patient whose clotting activity was greatly reduced by anticoagulant therapy. Localized hemorrhage by diapedesis is a common finding in the zone of an infarction regardless of whether the vascular obstruction is due to an embolism or a thrombosis. It is quite possible that an incident of this sort occurred in this patient. The chief hazard with anticoagulant therapy is the development of a hemorrhagic state, manifestations of which may develop spontaneously or seriously complicate other preexisting pathologic conditions.

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■ Although extremely numerous, the theories concerning the transmission of the sensitive impressions in the spinal cord may be considered as mere varieties of two principal ones, according to which the transmission takes place chiefly, or exclusively in the posterior columns, or in the gray matter. Longet is the principal advocate of the first of these two theories. He thinks:

1st. That all the nerve-fibres of the spinal nerves which are employed in the transmission of the sensitive impressions, enter the posterior columns of the spinal cord, and go up to the brain in these columns, and, therefore, that the Sensorium receives sensitive impressions only from these parts of the spinal cord, and their prolongations in the encephalon.

2nd. That the medulla oblongata, the restiform bodies being the direct continuations of the posterior columns of the spinal cord, are also the only channels for the transmission of the sensitive impressions.

3rd. That the sensitive impressions going to the sensorium have to pass chiefly across the cerebellum, as the restiform bodies chiefly pass across this organ.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System,* published in 1860.

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AMERICAN ACADEMY OF NEUROLOGY

Nielsen Becomes ANA President J. M. Nielsen of Los Angeles assumed the presidency of the American Neurological Association at the end of its eightieth annual meeting at the Palmer House in Chicago (June 13-15). Newly elected officers were: H. Houston Merritt, president-elect; James W. Kernohan, 1st vice-president; Robert B. Aird, 2nd vice-president; Charles Rupp, secretary-treasurer and editor of the transactions; and William F. Caveness, assistant secretary. Added to the council were Russell N. DeJong and Charles Rupp; Harvey Bartle, Jr. was elected ANA representative to the American Board of Psychiatry and Neurology. Arthur Leslie Drew, Jr., John Douglas French, and John Ignatius Nurnberger were elected to active membership. Ludo van Bogaert, Heinrich Pette, Georges Schaltenbrand, and Sir Francis M. R. Walshe were elected to honorary membership....One hundred and sixty members and 293 guests registered for the scientific sessions, which began with a symposium on "Electrical Activity of Subcortical Centers," introduced by President Percival Bailey in his presidential address on the "Localization of Consciousness."..... The annual banquet was held in the Red Lacquer Room of the Palmer House on June 14th, preceded by cocktails given by the Chicago Neurological Society and followed by entertainment provided by the Illinois Psychiatric Society.... The 1956 annual meeting will be held at the Claridge Hotel, Atlantic City, (June 18-20).

Canadian Neurologists Meet in Toronto With a large number of guests from the British Isles and the U.S.A., the Canadian Neurological Society held its seventh annual meeting in the Sunnybrook Hospital, Toronto (June 16-19). The scientific sessions began with a symposium (June 16) on "Centrencephalic Integration and the Brain-Stem Reticular System." Wilder Penfield officiated as chairman of the symposium and among the participants were H. W. Magoun, Denis Williams, William Cobb, J. A. V. Bates, and Herbert H. Jasper. The next morning President Francis L. McNaughton delivered a presidential address on the history of Canadian neurology. The remainder of the scientific sessions covered a wide range of topics of current interest in both clinical and basic neurology. A carefully

planned social program interspersed the scientific sessions: a cocktail party at the York Club; a supper and social evening in the scholarly setting of Trinity College, sparked by speeches and Scottish bagpipers; and the annual dinner, which was held at the Royal York Hotel.... Attending as guests of the society were members of the section of neurology of the Royal Society of Medicine, the Association of British Neurologists, and the Society of British Neurological Surgeons, as well as representatives from American neurologic and neurosurgical societies, including Walter O. Klingman (AAN), H. Houston Merritt (ANA), and Edgar Kahn (Harvey Cushing Society).... The newly elected president of the Canadian Neurological Society is Jean Sirois (Quebec), and the secretary-treasurer, J. L. Silversides (Toronto); the 1956 meeting will be held in Quebec City.

XXth International Reunion Held in Paris

On June 7 and 8, in the Ecole des infirmieres of the Salpetriere, the XXth International Neurological Reunion was held under the auspices of the French Neurological Society (Societe Francaise de Neurologie). The reunion program highlighted a symposium on the neurologic aspects of collagen diseases (June 7), under the chairmanship of Prof. Raymond Garcin, and an official ceremony (June 8) for the presentation by Prof G. Guillain of a commemorative volume (Livre Jubilaire) to Dr. Andre-Thomas for 50 years of distinguished service. The latter function was inaugurated with an address by Dr. M. P. Mathieu, president of the French Neurological Society, after which speeches were given by Dr. M.-A. Durupt on behalf of former pupils of Dr. Andre-Thomas, by Prof. L. van Bogaert on behalf of foreign neurologists, and by Prof. A. Baudouin on behalf of the National Academy of Medicine. These ceremonies were followed on the same day by the unveiling of a plaque bearing the name of Dr. Andre-Thomas to be installed in his consultation room in the Hospital of Saint Joseph.... On June 9, the XXth International Neurological Reunion was followed by the regular monthly meeting of the French Neurological Society, 12, rue de Seine.

Spanish Neurologists to Honor Centenary of L. Barraquer Roviralto

On October 15th, Spanish neurologists and guests will convene in Barcelona to celebrate the centenary of Dr. Luis Barraquer Roviralto, generally regarded as the founder of clinical neurology in Spain. A distinguished teacher, Dr. Roviralto, is also the author of many neurologic treatises, particularly those concerned with neuromuscular functions. He founded, in 1882, the Neurological Service of Santa Cruz Hospital in Barcelona, which now is the Neurological School of Santa Cruz y San Pablo Hospital, and is presently directed by his son, L. Barraquer Ferre. All communications regarding the cen-

tenary should be forwarded to the Secretary General, Dr. L. Barraquer Bordas, Lauria, 102, Barcelona, a grandson of Dr. L. Barraquer Roviralto.

Masland Surveying Research in Mental Retardation Richard L. Masland, professor of neurology at Bowman Gray School of Medicine, has obtained leave of absence from his academic post to become director of research of the National Association for Retarded Children. In his new assignment, Dr. Masland has begun a fact-finding survey of the present status of research in mental retardation. To accomplish his objective, Masland divides his program into three phases: an orientation phase to review the significant literature on mental retardation and consult with research directors and foundations now supporting research in this field; a second phase concerned primarily with direct consultation with principal investigators in leading centers of the country in order to construct a cross-sectional picture of current research in mental retardation; and a third phase involving a search for promising areas of research in this field with the view toward their further implementation in the future. The time estimated for the study is one to two years.

Three-Year Training Program At Yale Gilbert H. Glaser, associate professor of medicine (neurology), announces that a three-year training program in neurology at the Yale University School of Medicine has been approved by the Council on Education of the American Medical Association. Under this program, special opportunities are also available for training in clinical neurophysiology, neuropathology, and pediatric neurology. A clinical fellowship, carrying a stipend of $3,600 per year, is open to suitable applicants.

Lasater Goes to Tennessee Gene M. Lasater, formerly instructor in neurology at the University of Minnesota and chief of the neurological section, Fifth General Hospital, Stuttgart, Germany, has gone to the University of Tennessee College of Medicine as a full-time assistant professor of neurology, to assist in organizing a department of neurology and to conduct research in neurologic disorders.

Prize in Multiple Sclerosis Dr. Samuel Abrahams, in honor of his brother, Mr. Harry Abrahams, has established a prize of $350 for papers on studies in multiple sclerosis. The first prize is $200 and the second prize is $150. Persons wishing to submit a manuscript should write to the secretary of the Chicago Neurological Society, Dr. Oscar Sugar, 912 South Wood

Street, Chicago 12. The winning papers will be read at one of the regular meetings of this society.

Program Committee To Meet In Brussels The American Program Executive Committee for the Sixth International Neurological Congress will convene with their foreign counterparts in Brussels, September 7 and 8, to formulate tentative plans for the Sixth International Neurological Congress to be held in the same city during the second half of July 1957. Members of the American Program Committee are: Henry Alsop Riley, chairman; Pearce Bailey, Paul C. Bucy, Horace W. Magoun, H. Houston Merritt, and A. Earl Walker. Also planning to meet in Brussels around the time of the 1957 Congress are the International Congress for Electroencephalography and the International League Against Epilepsy. The president of the Sixth International Neurological Congress is Dr. Ludo van Bogaert, Institute Bunge, Antwerp, 50, rue Philip Williot.

Briefs Robert Wartenberg has been elected an honorary member of the Argentine Society of Neurology, Psychiatry, and Neurosurgery.... The 18th session of the Medical Advisory Board of the National Multiple Sclerosis Society was held at the Conrad Hilton Hotel in Chicago prior to the meeting of the American Neurological Association. Augustus S. Rose succeeded Hans H. Reese as chairman of the Multiple Sclerosis Society's Medical Advisory Board at the end of the meeting.... Dedication ceremonies of the Armed Forces Institute of Pathology in the Walter Reed Army Medical Center were held on May 26th.

Pearce Bailey

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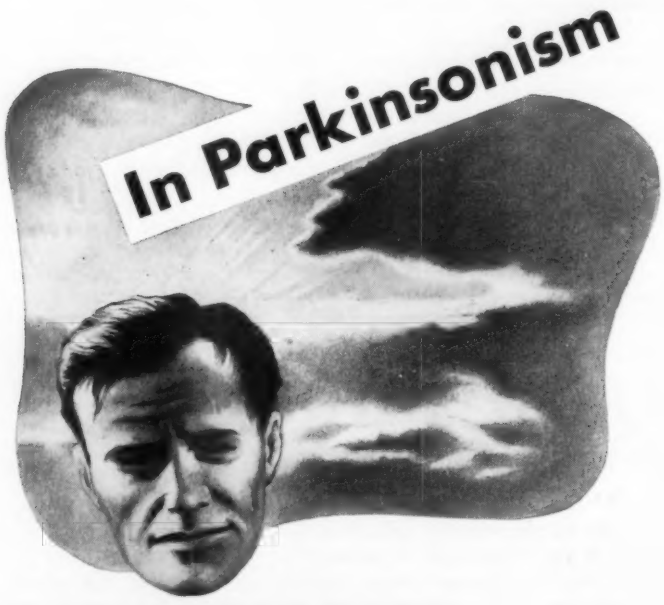

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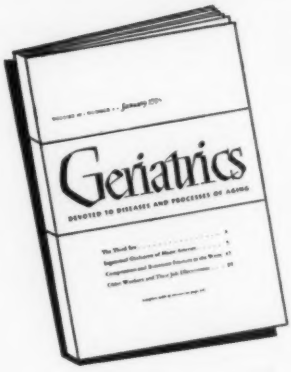

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*Combes, F. C. & Canizares, O.: New York St. J. Med. 52:706, 1952; Marsh, W. C.: U. S. Armed Forces M. J. 1:1045, 1950.

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